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VOLUME 65

1940

PUBLISHERS

AMERICAN MEDICAL ASSOCIATION

CHICAGO, ILL.

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VOLUME 65 JANUARY 1940 NUMBER 1

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TREATMENT OF MULTIPLE SCLEROSIS WITH NICOTINIC ACID AND VITAMIN B_1

PRELIMINARY REPORT

MATTHEW T. MOORE, M.D.

PHILADELPHIA

The treatment of advanced multiple sclerosis with nicotinic acid and a combination of nicotinic acid and thiamin chloride has yielded promising results in cases in which the patients have failed to respond to therapies hitherto used. While complete remission has not been obtained, the use of the treatment suggested here has resulted in continued symptomatic improvement. The potential value of the suggested treatment may be judged in the light of prevailing conceptions of the etiology and treatment of multiple sclerosis.

From 1838, when Sir Robert Carswell, as cited by Putnam,[1] first described the pathology of multiple sclerosis, up to the present, the treatment of this disease has been entirely empiric. When one examines the diversity of remedial agents and methods employed, it becomes evident that the disarray is occasioned by complete ignorance of the etiology of the disease, coupled with the desire to find a remedy for one of the most perplexing and frequently occurring nervous ailments.[2]

Many hypotheses have been advanced regarding the etiology of multiple sclerosis; endotoxins and exotoxins,[3] specific organisms,[4] virus

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Read before the Philadelphia Neurological Society, May 26, 1939.

From the Jewish Hospital and the John L. Eckel Neuropathological Laboratory, University of Pennsylvania Graduate School of Medicine.

1. Putnam, T. J.: The Centenary of Multiple Sclerosis, Arch. Neurol. & Psychiat. **40**:806 (Oct.) 1938.

2. Brain, W. R.: Critical Review: Disseminated Sclerosis, Quart. J. Med. **23**:343 (April) 1930. Problems of Disseminated Sclerosis, editorial, J. Neurol. & Psychopath. **13**:227 (Jan.) 1933.

3. (*a*) Hassin, G.: The Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **7**:589 (May) 1922. (*b*) Brickner, R. M.: Studies on the Pathogenesis of Multiple Sclerosis, ibid. **23**:715 (April) 1930. (*c*) Jelliffe, S. E., and White, W. A.: Diseases of the Nervous System, Philadelphia, Lea & Febiger, 1923, p. 562. (*d*) Steiner, G.: Multiple Sclerosis: The Etiological Significance of the Regional and Occupational Incidence, J. Nerv. & Ment. Dis. **88**:42 (July) 1938.

(Footnote continued on next page)

infection,[5] trauma,[5c] vascular disturbances [6] and vitamin deficiency [7] are some of the many factors which have been charged with producing the disease. The variety and uncertainty of the etiologic theories advanced are reflected in the forms of treatment which have been used. Gowers,[8] in 1888, suggested the use of arsenic, silver nitrate and quinine; Oppenheim,[9] in 1908, recommended Credé's silver ointment,[10] application of the galvanic current to the back or head, local blood letting (by leeches) and Nauheim baths. Brickner,[11] in an excellent summary of the therapy of multiple sclerosis, listed an imposing array of remedies, including, among others, various preparations of antimony and arsenic, fever induced by various methods (diathermy, malaria, typhoid vaccine), fever in conjunction with drugs, surgical procedures (cervical sympathectomy, root section, etc.), germanin (reported to be a sodium salt of sym. bis. [*m*-aminobenzoyl-*m*-amino-*p*-methylbenzoyl-*l*-naphthylamino-4,6,8-trisulfonic acid] urea), serums, hypnotism, intraspinal injection of lecithin, vaccines and quinine hydrochloride.

Recently, emphasis has been laid etiologically on the possible implications [6] of vascular lesions and therapeutically on the employment of fever therapy to promote hyperemia and an increased flow of blood in nerve tissue. The application of fever therapy in its various forms (malaria, typhoid vaccine, hot baths, diathermy, the Kettering hypertherm) has many annoying disadvantages, and indeed dangers,[12] which should make welcome a less disturbing method of inducing the changes wrought by

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4. Bullock, W. E.: The Experimental Transmission of Disseminated Sclerosis, Lancet **2**:1185, 1913. Steiner, G.: Multiple Sklerose, Therap. Halbmonatsh. **34**:68 (Feb. 1) 1920. Schuster, G.: Spirochetes in the Etiology of Certain Paralyses, Lancet **1**:21 (Jan. 1) 1921.

5. Chevassut, K.: Aetiology of Disseminated Sclerosis, Lancet **1**:552 (March 15) 1930. Purves-Stewart, J.: A Specific Vaccine Treatment in Disseminated Sclerosis, ibid. **1**:560 (March 15) 1930.

6. Putnam, T. J.: The Pathogenesis of Multiple Sclerosis: A Possible Vascular Factor, New England J. Med. **209**:876 (Oct. 19) 1933; Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298 (June) 1937.

7. Zimmerman, H. M., and Burack, E.: Lesions of the Nervous System Resulting from a Deficiency of the Vitamin B Complex, Arch. Path. **13**:207 (Feb.) 1932.

8. Gowers, W. R.: A Manual of Diseases of the Nervous System, Philadelphia, P. Blakiston, Son & Co., 1888, p. 930.

9. Oppenheim, H.: Text-Book of Nervous Diseases, translated by A. Bruce, ed. 5, Edinburgh, Otto Schulze & Co., 1911, vol. 1, pp. 33 and 350.

10. Credé's ointment contains 15 per cent of collargol (a proprietary preparation of colloidal silver and silver nitrate, stabilized by egg albumin), 5 per cent of water, 10 per cent of white wax and 70 per cent of benzoinated lard.

11. Brickner, R. M.: A Critique of Therapy in Multiple Sclerosis, Bull. Neurol. Inst. New York **4**:665 (April) 1936.

this treatment. Smith, Ruffin and Smith [13] reported the successful treatment of pellagra with nicotinic acid and described the reaction following the intramuscular administration of 60 mg. of nicotinic acid; "a marked flushing of the face, neck, chest and arms appeared a few minutes after intramuscular injection and lasted fifteen minutes." Similar flushing occurred after the intravenous use of the drug which had been dissolved in a solution of 5 per cent dextrose in physiologic solution of sodium chloride. No discomfort was experienced by the patient.

The description of marked flushing of the skin led me to consider the feasibility and advisability of using nicotinic acid in cases of multiple sclerosis and to attempt to determine whether the cerebrospinal nervous system becomes hyperemic in a manner similar to that observed in the skin. If the answer to this query were in the affirmative, some of the beneficial effects of fever therapy might be realized by the use of this substance and the baneful side effects eliminated.

MATERIAL AND METHOD

The 5 cases reported here represent, in the main, advanced multiple sclerosis. Nicotinic acid therapy was begun in the first case on Feb. 15, 1938, and has been used almost continuously, with a few interruptions, until the time of writing. Until June 1938 the nicotinic acid was given intramuscularly and intravenously on alternate week days. The intramuscular dose varied from 60 to 120 mg., dissolved in 10 cc. of sterile physiologic solution of sodium chloride. The intravenous dose varied from 60 to 160 mg., dissolved in 1,000 cc. of 5 per cent dextrose in sterile physiologic solution of sodium chloride, and was given over a period of approximately one hour. After June 4, 1938 the drug was given intramuscularly exclusively, in doses varying from 80 to 140 mg., two or three times weekly, depending on the patient's reaction. At this time the use of vitamin B_1 (thiamin chloride) was begun, and it was administered intravenously in doses of 3.32 mg. (10,000 international units) at the height of the cutaneous hyperemia. After July 18 the nicotinic acid and thiamin chloride were given combined in solution with sterile distilled water, each cubic centimeter representing 12 mg. of nicotinic acid and 3.32 mg. of thiamin chloride. Ten cubic centimeters of this solution was the average intramuscular dose, given into the buttocks. It was found that unless the solution was heated to about 110 F. and drawn into a warm syringe barrel immediately before injection the characteristic flushing of the skin and pervading body warmth did not develop with any degree of intensity.

In 2 cases thermocouple records of skin temperatures were made to determine the degree of hyperemia, and in addition (on another occasion) studies of the

12. (*a*) Bennett, A. E.: Evaluation of Artificial Fever Therapy for Neuropsychiatric Disorders, Arch. Neurol. & Psychiat. **40**:1141 (Dec.) 1938. (*b*) Collins, R. T.: Transitory Neurological Changes During Hyperthermia, Bull. Neurol. Inst. New York **7**:291 (Dec.) 1938.

13. Smith, D. T.; Ruffin, J. M., and Smith, S. G.: Pellagra Successfully Treated with Nicotinic Acid: A Case Report, J. A. M. A. **109**:2054 (Dec. 18) 1937.

cerebrospinal fluid pressure (expressed in millimeters of cerebrospinal fluid) were made before and during the appearance of the skin reaction. Oral temperatures were also taken at this time. Electrocardiographic studies were performed on 3 patients before the use of nicotinic acid was begun and several months thereafter, to ascertain any changes attributable to its use.

As a result of the finding of increased cerebrospinal fluid pressures and in an attempt to answer the query originally posed regarding the possible hyperemia of the central nervous system following the use of nicotinic acid, preparations of the cat's brain and cervicothoracic portion of the cord were made to demonstrate the reaction of the pial vessels to intramuscular use of the drug. With the animal under anesthesia induced with sodium amytal (50 mg. per kilogram of body weight given intraperitoneally), the brain and spinal cord (lower cervical and upper thoracic portions) were exposed and the pial vessels photographed before and five and ten minutes after the intramuscular injection of 4 cc. (48 mg.) of a solution of nicotinic acid. The photographic technic with regard to intensity of light, distance and other factors was constant throughout. The photographs were enlarged 24 diameters to show any changes in the size of the arterial vessels and any increase in the number of vessels perceptible.

REPORT OF CASES

CASE 1.—E. N., a white man aged 38, married, gave the history of an onset of uncertain gait and ready fatigability in June 1933. Because of incoordination and easy fatigue he was compelled to quit his work in the delivery room of a newspaper. When first examined by me in June 1934, he showed bilateral temporal pallor of the optic disks; nystagmus on horizontal and vertical gaze; thick spastic speech; exaggerated tendon reflexes in the upper and lower limbs; loss of abdominal reflexes; diminished cremasteric reflexes; bilateral Hoffmann, Babinski, Chaddock and Oppenheim signs; loss of vibration sense in the malleoli of both feet; impairment of the senses of position and passive motion in the lower limbs, and a spastic, dancing gait. Examination of the cerebrospinal fluid showed 5 cells per cubic millimeter, a negative Wassermann reaction, a colloidal gold curve characteristic of dementia paralytica and 20 mg. of protein. Hematologic studies and the Wassermann test of the blood gave normal results. Other laboratory studies revealed nothing abnormal. The patient was placed on a high vitamin diet and given quinine bisulfate, 5 grains (0.325 Gm.), two or four times a day, for over two months, without showing appreciable change. During August 1934 he began the first series of ten weekly treatments with the Kettering hypertherm. The usual procedure for inducing hyperpyrexia was followed in this and in subsequent treatments. Slight subjective improvement lasted about one month, followed by a decline. A second series of eleven treatments with the Kettering hypertherm was given in 1935, after which there was improvement in speech. Two more series of inductions of hyperpyrexia were given, beginning May 1936 and January 1937, respectively, the total number of treatments being thirty-nine. His condition became progressively worse, and he was compelled to use an improvised walker to get about. In addition to intensification of the findings at the first examination, there were a positive Romberg sign, bilateral ankle clonus, intention tremor and marked difficulty in arising from the seated position and in sitting down. Five cubic centimeters of histidine monohydrochloride (larostidin) was given daily intramuscularly from April 27 to May 7, 1937, without change.

On Feb. 15, 1938, he was given for the first time 60 mg. of nicotinic acid dissolved in 10 cc. of sterile physiologic solution of sodium chloride, injected into the buttock. In three minutes there was a subjective feeling of warmth in the face and neck, and in five minutes flushing of the face, neck and shoulders appeared, extending later to the chest and back. This flushed appearance lasted forty-five minutes. There was no appreciable change in pulse or blood pressure. Oral temperatures taken at the time of flushing showed no rise above normal. The patient was given intramuscular and intravenous injections alternately on week days until June 4, 1938. The intravenous injections consisted of 120 mg. of nicotinic acid dissolved in 1,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride, which was given over a period of one hour. With intravenous administration the flushing did not appear as rapidly or as intensely as with intramuscular injection. By June there was considerable subjective and

TABLE 1.—*Thermocouple Readings of Skin Temperature (Case 1) Following Intravenous Injection of 1,000 Cc. of 5 per Cent Dextrose in Physiologic Solution of Sodium Chloride Containing 140 Mg. of Nicotinic Acid*

Skin Temperature, Degrees, C.	Forehead	Lobe Left Ear	Lobe Right Ear	Left Zygoma	Right Zygoma	Anterior Portion of Neck	Left Shoulder	Right Shoulder	Dorsum of Third Finger	Chest, Left Side	Chest, Right Side
Before injection....	32.0	32.0	31.0	34.0	34.3	34.1	33.4	33.1	33.5	32.8	32.8
10 min. after injection.....	33.0	34.0	34.0	35.0	35.2	35.0	34.3	33.8	33.8	33.4	33.6
12 min. after injection.....	35.2	35.2	35.2	35.8	35.8	35.8	34.0	34.3	34.0	34.2	34.2
14 min. after injection.....	35.3	35.5	35.5	35.8	35.8	35.6	34.5	34.6	34.0	34.3	34.3
Maximum rise.....	3.3	3.5	4.5	1.8	1.5	1.7	1.1	1.5	0.5	1.5	1.5

objective improvement. Subjectively, the patient noted greater ease of movements and less stiffness of his limbs; there was also improvement in the gnostic sense. He was able to walk without the aid of the walker and arose from the sitting position with less difficulty than previously. Coordination had improved, as shown by the various tests. On June 4 vitamin B_1 (thiamin chloride) therapy was begun. Injections of 10,000 international units of crystalline vitamin B_1 (33.2 mg. of thiamin chloride) dissolved in 1 cc. of sterile distilled water were given intravenously at the height of the skin flushing. This was done three times a week until July 18, 1938, when the thiamin chloride (33.2 mg.) was combined with nicotinic acid (120 mg.) in 10 cc. of sterile distilled water and given intramuscularly. On September 8 therapy was discontinued for three weeks to see if any change occurred. The patient began to show return of the marked spasticity and was compelled to resort to use of the walker. He complained of difficulty in moving his body and in sitting and arising. When the nicotinic acid and vitamin B_1 therapy was renewed he noted improvement within several days. Complete remission was not obtained, but he felt distinctly better able to walk and maneuver his body than previous to this form of medication. Laboratory studies

of the urine and blood gave essentially normal results. Roentgen studies showed that the skull and vertebral column were entirely normal. Repeated Queckenstedt tests revealed no evidence of cerebrospinal fluid block. Electrocardiographic studies made prior to the use of nicotinic acid and again on October 21 showed no appreciable difference in the tracings. Thermocouple readings of skin temperature taken on May 25, 1938, when an intravenous injection of 1,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride containing 140 mg. of nicotinic acid was given, are shown in table 1. On October 15 a lumbar puncture was performed, with the patient in the recumbent position, and pressure readings,

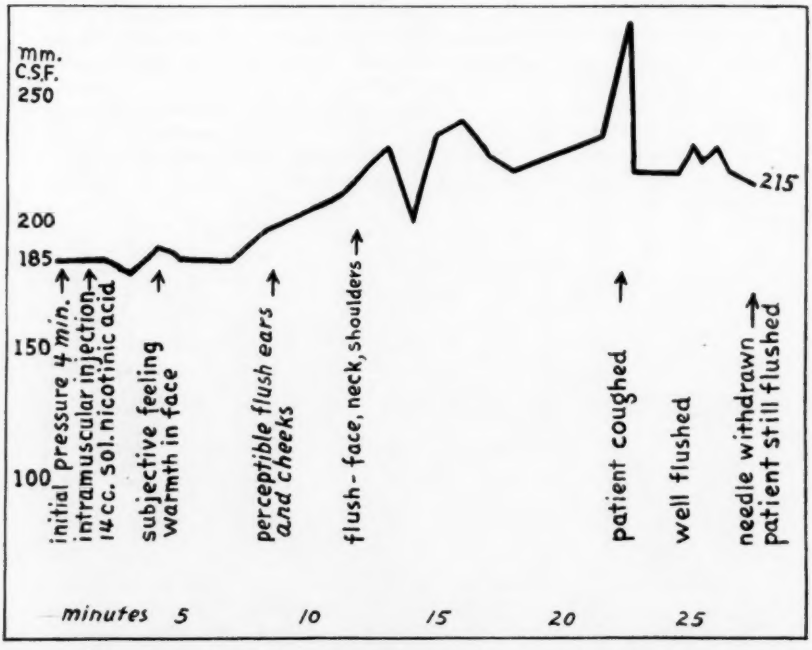

Fig. 1 (case 1).—Manometric readings showing a sustained rise of cerebrospinal fluid pressure coincident with the active flushing of the skin following intramuscular injection of a solution of 168 mg. of nicotinic acid.

expressed in millimeters, of cerebrospinal fluid, were made at thirty second intervals for twenty-five minutes; the pressures were noted previous to and after the intramuscular injection of 14 cc. of a solution containing 12 mg. of nicotinic acid per cubic centimeter of distilled water.

CASE 2.—E. I., a white woman aged 47, a housewife, first noticed difficulty in walking during the summer of 1934. At first her left leg gave way under her, and then both legs became involved. She tired easily when walking and experienced an occasional "peculiar numbness" of her lower limbs. At times she felt an electric-like sensation along her spine. She also complained of urgency in

urination. She received manipulative treatments, but despite this her condition became worse. When I first examined her in October 1935, she complained of the symptoms mentioned, plus difficulty in playing the piano because of slight stiffness of her fingers. Examination showed temporal pallor of both optic disks; incoordination in the finger to nose test; exaggerated biceps and triceps reflexes, more marked on the left; a Hoffmann sign bilaterally, that on the left side predominating; absence of abdominal reflexes; exaggerated knee jerks and a more marked ankle jerk on the left; a Babinski sign and ankle clonus bilaterally, and a spastic ataxic gait. Laboratory studies performed in December 1935 showed that the blood and urine were normal; the Queckenstedt test revealed no evidence of cerebrospinal fluid block; examination of the cerebrospinal fluid showed 10 cells per cubic millimeter, a negative Wassermann reaction, a colloidal gold curve of 1123220000 and a negative Wassermann reaction of the blood. Roentgenographic studies of the skull and vertebral column showed nothing abnormal. The patient was given a series of hyperpyrexia treatments, typhoid vaccine being given intravenously; in addition, forced cerebrospinal fluid drainage was carried out by the method of Retan. There was a moderate degree of improvement for several months in the subjective feeling of less stiffness of the limbs and in walking. Later there was a gradual decline, however, and quinine bisulfate was given in doses of 10 to 20 grains (0.65 to 1.3 Gm.) daily, depending on the degree of tolerance. No appreciable subjective or objective change was noticed; in fact during July 1936 complete paraplegia developed, lasting three weeks, from which the patient slowly recovered. Several alternating courses of bismuth, mercury and iodides produced no change. Again during the summer of 1937 marked difficulty in standing developed, the patient being unable to walk, and she was entirely unable to play the piano. There were extreme incoordination and ataxia. A second series of hyperpyrexia treatments with typhoid vaccine failed to alter the downhill course.

On March 3, 1938, treatment with nicotinic acid was begun, and the method of injection outlined under "Material and Method" was carried out. A description by the patient of the sensations she experienced after an injection of nicotinic acid and vitamin B_1 follows.

"Within a few seconds to half a minute there is a sulfur-like taste in the mouth. Three minutes after injection a flush begins in the face, accompanied by a hot, prickly sensation; it spreads quickly to the chest; thence it begins creeping down the arms to the elbows, then on down to the finger tips—the third finger in each hand feeling it especially, a tingling with tight sensation at the tip. It continues creeping down the body to the hips. In fifteen minutes the tingling sensation reaches the knees and begins to recede from the face and to increase in the lower limbs; the knees are hot, but the ankles are cold. The tingling sensation begins in the feet, though the feet are still cold. Marked stiffness in the legs begins. In twenty-five minutes the legs below the knees begin to feel hot. In thirty minutes the feet begin to get hot and prickly. The face is still flushed, but tingling is only slight. In forty-five minutes the sensation of heat is still increasing. In one hour the legs are extremely stiff and hot. There is slight headache. The flush has gone from the face and chest. There is loss of appetite. At two hours, after arising, there is an odd sensation along the spinal column, such as when the back is very tired. Otherwise the condition is unchanged. The sensation of heat is still increasing in the feet after two and a half hours. After five or six hours the lower limbs are just comfortably warm. By the following afternoon the stiffness in the lower limbs begins to wear off. After injection there is noticeable absence of pains in the legs and ankles; there is a stretchy, pully feeling during the night; a sensation of 'going to sleep' comes on after sitting still for a while."

Within two weeks after treatment was instituted she noticed improvement in walking and began to regain her ability to play the piano. The sensation of numbness of her lower limbs disappeared within six to eight weeks. On two occasions therapy was stopped for two weeks in order to determine if any change would occur. During one of these interludes injections of sterile distilled water were substituted. During each two week interval there were a definite increase in spasticity of the four limbs, great difficulty in walking and increased incoordination and ataxia of the upper limbs. She insisted that a change for the worse had taken place. On returning to the use of nicotinic acid and thiamin chloride she noticed appreciable lessening of spasticity, and at the time of writing she can play the piano fairly well and walk about the house, albeit in a spastic manner. The exaggerated tendon reflex activity, pathologic reflexes and sensory changes have not altered. Disturbances of the bowel or bladder have not supervened.

Case 3.—A. L., a white woman aged 49, in 1928 noticed unsteadiness of gait, which was followed in a short time by inability to walk without assistance. Speech difficulty developed. Examination showed a labored, spastic gait and dragging of both feet when using an improvised supportive walker (she was unable to walk without its aid), incoordination and ataxia of the upper limbs, exaggerated tendon reflexes throughout, absence of abdominal reflexes, a Babinski sign bilaterally and marked pallor of the temporal aspects of both disks. She had great difficulty in moving her body and in getting out of bed. In February 1937 she was given quinine bisulfate, 5 grains (0.325 Gm.), three times a day for approximately three months, without improvement. Later histidine monohydrochloride, 5 cc. intramuscularly, was given daily for two months, and no improvement was noted. On March 1, 1938 nicotinic acid therapy was begun and carried out in a manner similar to that in the preceding cases. The cutaneous reaction to nicotinic acid was much the same as in case 1. There was no rise of oral temperature during the height of flushing of the skin. When thiamin chloride was added the patient noticed a peculiar taste in her mouth, but was unable to describe it. She began to notice improvement in walking about one month after therapy was begun. She stated that she no longer dragged her feet so much and was able to bend her legs at the knees and lift her feet from the ground. Later she noticed ease in moving her body and was elated about it. Changes in the objective neurologic signs were not noticed. This patient had invariably refused previous forms of treatment after a few months' trial when they failed to reward her with improvement, but she welcomed the injections of nicotinic acid and vitamin B_1 and requested their continuance.

Laboratory studies gave essentially normal results. Electrocardiographic studies, made on March 4 and Oct. 20, 1938, showed no change in the tracings on the two dates.

Case 4.—M. P., a white man aged 32, formerly an electrician, dated his illness from 1927, when he complained of severe pains in the back of his neck. Shortly afterward staggering and uncertainty in walking appeared. The legs became stiff, and bladder disturbance appeared early in the course of the disease and has been present since. Speech difficulty began in 1930. He became increasingly spastic, and involvement of the arms recently developed. For the past one and a half years he has been unable to walk and uses a wheel chair.

In 1928 his condition was diagnosed as multiple sclerosis at a hospital for neurologic diseases, and germanin was administered from September 1928 to July 1929, without improvement. He was later treated at five other institutions, before entering the Jewish Hospital in April 1938. He had received quinine

bisulfate and hyperpyrexia treatments with diathermy and the Kettering hypertherm, and had been placed on a dehydration regimen, but at no time was a remission induced.

In April 1938 he presented a picture of extreme boardlike spasticity of the lower limbs, which usually were crossed and which could not be uncrossed voluntarily. He had great difficulty in moving in bed and was unable to lift himself from the recumbent position. There were bilateral nystagmus, lateral and vertical; pallor of both disks; intention tremor; scanning speech; exaggerated biceps and triceps reflexes bilaterally; absence of cremasteric reflexes; spasticity of the legs so marked at times as to make it impossible to obtain the knee jerks, or to make them, when obtainable, greatly exaggerated; bilateral Babinski and Chaddock signs, and loss of sense of vibration and passive motion in the lower limbs. Hematologic studies, urinalysis, a Wassermann test of the blood and cerebrospinal fluid studies gave normal results. The Queckenstedt reaction was negative. Roentgenographic studies of the skull and vertebral column and pneumomyelographic

TABLE 2.—*Thermocouple Readings of Skin Temperature (Case 4) Following Intramuscular Injection of 10 Cc. of a Solution of Nicotinic Acid*

Skin Temperature, Degrees, C.	Forehead	Lobe Right Ear	Lobe Left Ear	Right Malar Area	Left Malar Area	Anterior Portion of Neck	Right Shoulder	Left Shoulder	Right Side of Abdomen	Left Side of Abdomen	Dorsum, Right Hand	Dorsum, Left Hand	Right Knee	Left Knee
Before injection.....	35.4	32.2	33.4	35.4	35.6	36.2	35.4	35.4	35.4	35.4	34.2	34.8	34.4	33.4
12 min. after injection..	35.9	35.4	36.4	36.4	36.6	36.4	36.2	36.2	35.8	35.8	34.4	35.6	34.8	33.8
17 min. after injection..	37.4	35.4	36.4	37.6	37.8	37.4	36.6	36.4	36.2	36.4	35.6	36.4	35.4	34.6
22 min. after injection..	37.4	35.6	36.6	37.8	37.8	37.8	36.8	36.4	36.6	36.6	36.4	36.8	35.6	34.8
27 min. after injection..	38.2	36.6	37.4	38.4	37.6	37.4	36.8	36.2	36.4	36.6	36.8	36.8	35.6	35.2
32 min. after injection..	37.4	36.2	36.2	37.4	37.4	36.8	37.2	36.2	35.8	35.8	36.4	36.4	35.4	34.8
Maximum rise.....	2.8	4.4	4.0	3.0	2.2	1.6	1.8	1.0	1.2	1.2	2.6	2.0	1.2	1.8

examination gave normal results. In the latter part of April 1938 vitamin B therapy was begun as outlined in the preceding cases. After injection of nicotinic acid there developed, beginning in about three minutes, redness of the face and neck and patchy flushing of the shoulders, arms and trunk and even the legs, the most intense of any of the reactions in patients receiving the drug. The first evidence of change was a subjective feeling of relaxation of the trunk and greater ease in moving his body. This occurred in June 1938, and in July he was able to uncross his legs voluntarily and to move them somewhat. His arms became less stiff, so that he could manipulate his wheel chair with increased facility. He managed to lift himself up in bed and to get in and out of bed, which previously was impossible. He invariably requested that the injections be continued after a brief interruption of treatment. The improvement has been limited thus far to a definite subjective feeling of lessening of rigidity and the objective finding of diminished spasticity of the lower limbs and trunk and improved coordination of the upper limbs. He is now able for the first time in years to stand while holding on to the bedstead. The pathologic neurologic signs are unchanged. Electrocardiograms taken on April 26 and Oct. 20, 1938, showed no difference in the tracings as the result of treatment.

Case 5.—J. D., a white man aged 29, a hardwood finisher by trade, noticed difficulty in walking in January 1935. The right leg was affected first, and he experienced numbness of the tips of the fingers of the left hand. In February 1935 he entered a hospital, where he received ten treatments with the Kettering

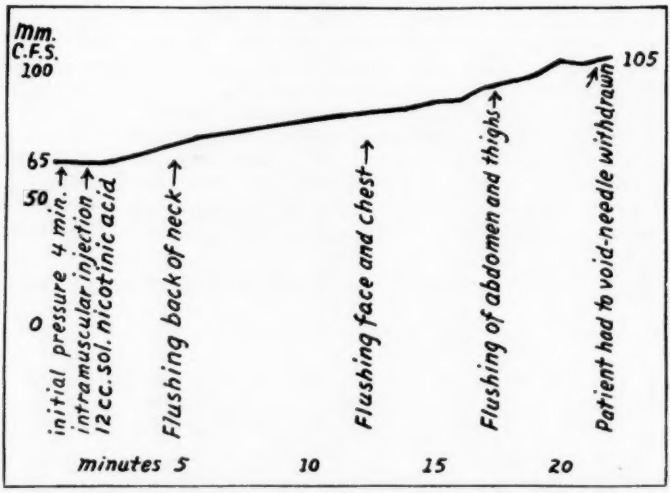

Fig. 2 (case 4).—Manometric readings following the intramuscular injection of 10 cc. of a solution of nicotinic acid (120 mg.), showing the rise of cerebrospinal fluid pressure during the time of active flushing of the skin.

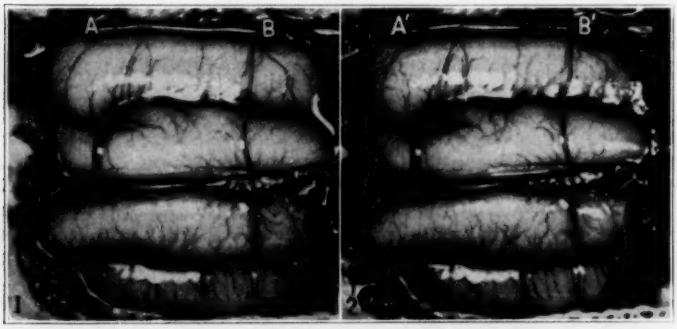

Fig. 3.—*1*, surface of a cat's brain before injection of nicotinic acid. *2*, five minutes after the intramuscular injection of 48 mg. of nicotinic acid. Note the increased caliber of the large vessels and the duskiness of the cortex, due to the increased capillary filling.

hypertherm. After leaving the hospital the left leg became stiff and weak; the right hand "curled up," and he had difficulty in straightening it. Both legs drew up and were very stiff. He had difficulty in starting the urinary stream and

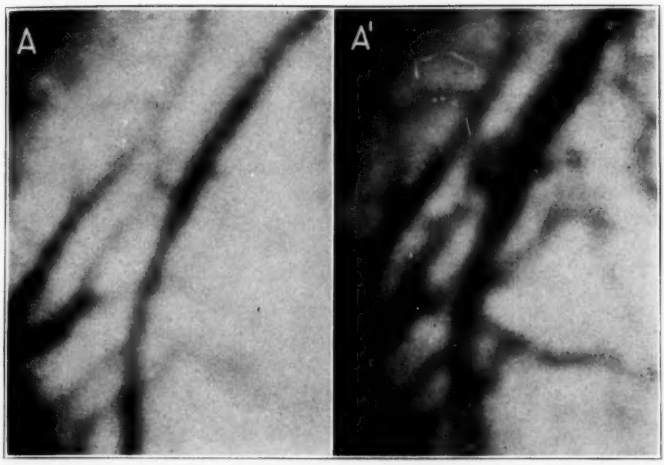

Fig. 4.—*A*, enlargement (24 diameters) of the pial artery shown in figure 3, *1 A*. *A'*, the same vessei five minutes after intramuscular injection of 48 mg. of nicotinic acid. There is not only an increase in the diameter of the arteries but an increased blood flow, as indicated by the photographic density of the arteries. Note also the increased number of smaller vessels visible.

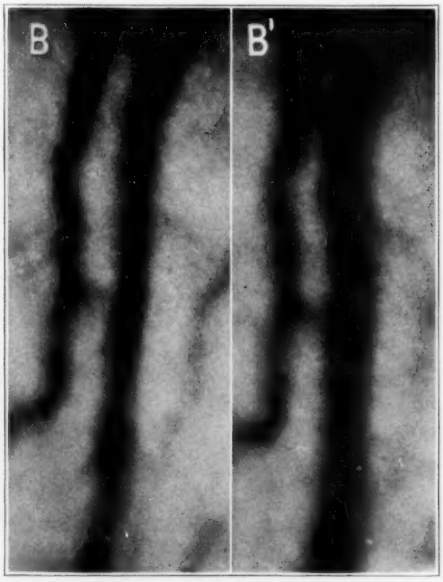

Fig. 5.—*B*, enlargement (24 diameters) of the pial artery shown in figure 3, *1 B*. *B'*, the same vessel five minutes after injection of nicotinic acid.

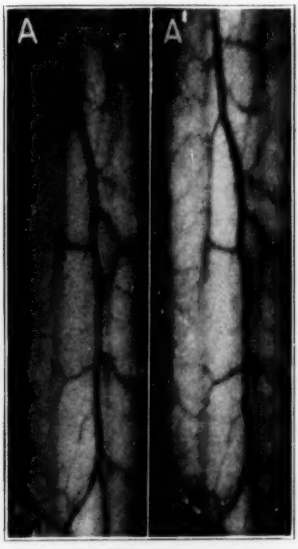

Fig. 6.—*A*, vessels on the doral aspect of the spinal cord previous to the injection of nicotinic acid. *A'*, same vessels as those shown in *A* ten minutes after the intramuscular injection of 48 mg. of nicotinic acid.

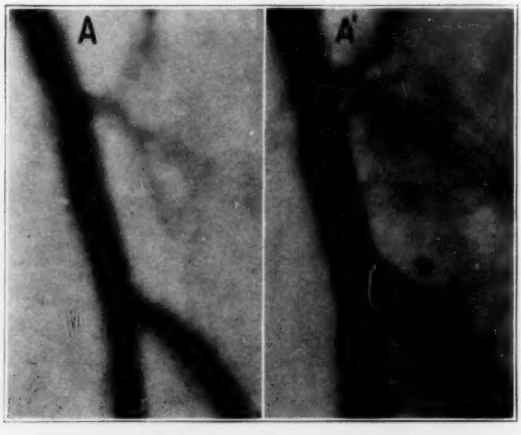

Fig. 7.—*A*, enlargement (24 diameters) of the vessel shown in figure 6 *A*. *A'*, enlargement (24 diameters) of the same vessel ten minutes after the injection of nicotinic acid.

trouble with his bowels. He entered another hospital, where he again was given ten hyperpyrexia treatments, without benefit. On May 24, 1938, he entered the Jewish Hospital. He then complained of marked stiffness of both legs, inability to walk or to move his body while in bed, weakness of both hands, numbness of both legs, "as if they were dead" and an electric-like sensation down his back, as well as the symptoms already enumerated. The significant neurologic findings were: temporal pallor of the right disk; atrophy of the intrinsic muscles of both hands; atrophy of the right forearm; marked weakness of both hands, with poor hand grip; incoordination of both upper limbs; exaggerated biceps and triceps reflexes; a Hoffmann sign bilaterally; absence of abdominal reflexes; exaggerated patellar and achilles reflexes bilaterally; bilateral Babinski and Chaddock signs; bilateral ankle clonus; spontaneous clonus of both legs whenever he attempted to lift himself in bed; loss of the senses of vibration and position in the lower limbs; foot drop, and inability to move his toes. He was unable to use his arms in feeding or dressing himself and could not hold a cigaret when he desired to smoke. Hematologic studies, urinalysis, serologic tests and examination of the spinal fluid gave normal results. The Queckenstedt reaction was negative. Roentgen studies of the skull and entire vertebral column showed no abnormalities.

Treatment with nicotinic acid was begun May 31, 1938, and the combined nicotinic acid–vitamin B_1 therapy was started on June 9. Within one week he noticed increased strength in his hand grip, and he had begun to move his toes. By July 9 he was able to move his body freely and was able to sit up in bed and in an armchair. The marked rigidity of the legs had diminished greatly. He stopped treatment for two months, and during this time there was considerable regression, but not to his previous state. Treatment was resumed Sept. 10, 1938, with three injections weekly. He noticed improvement in a short time, with decrease in spasticity and cessation of the electric-like sensation in his spine, and for the first time he was able to use his hands in eating, smoking and dressing. He stated that with this form of treatment he had greater use of his limbs and body than at any time since he completed his first series of hyperpyrexia treatments, in the spring of 1935. This patient noted also the sulfur-like taste within eight to fifteen seconds after injection of the mixed drugs.

COMMENT

The disease in the cases described may be classified as belonging to the intermediate and helpless stages, and as being of the chronic progressive type without remissions.[11] Prior to the use of nicotinic acid and vitamin B_1, the patients received in the aggregate the following forms of treatment: quinine bisulfate; germanin; high vitamin diet; hyperpyrexia (typhoid vaccine intravenously, diathermy, Kettering hypertherm); forced cerebrospinal fluid drainage, and histidine monohydrochloride.

Of the various therapies employed, hyperpyrexia appeared to produce a temporary improvement in most instances, except in case 5, in which the patient was made worse. In no instance did hyperpyrexia consummate a remission. In fact, after the short-lived improvement the patients stated that there was a noticeable decline in their ability to get about. It is evident that certain biochemical and physiologic changes occur incident to fever therapy, irrespective of the method of induction, which

bring about improvement during the course of the treatment and for a short time thereafter. Bennett [12a] stated:

> The common denominator of all methods, whether employing infectious, biologic, chemical or physical means, is simply increased body temperature or artificial fever . . . Fever per se increases the velocity of the blood, produces vasodilation and elevates the basal metabolism.

Regarding the use of fever in treatment of multiple sclerosis, Bennett [12a] said:

> Artificial fever therapy produces no permanent therapeutic effects which alter the course of the disease. In certain early stages of the disease it may produce transient temporary remissions, but in advanced stages it is of little or no value and may do harm.

This conclusion was not shared by such investigators as Stephenson,[14] Dreyfus and Mayer,[15] Schmidt and Weiss,[16] Neymann and Osborne [17] and Weiss,[18] who presented a more optimistic picture of the results obtained by hyperpyrexia. The factors of vasodilatation and increased blood flow, as observed in fever therapy, result in an increase in tissue oxidation and nutrition.

Vasodilatation and increased blood velocity affecting the brain and spinal cord may be induced by ganglionectomy and sympathectomy. Favorable results have been reported by Wetherell,[19] Royle [20] and Koch and de Savitsch.[21] In fever therapy the process of vasodilatation and increased blood velocity is essentially a generalized one, whereas after ganglionectomy or sympathectomy the resultant vasodilatation lies within the area supplied by the removed stellate or sympathetic ganglia. The beneficial effects of vasodilatation and increased blood flow achieved by fever therapy and sympathectomy can be obtained through the use

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14. Stephenson, J.: Diathermy in Multiple Sclerosis: Report of Progress, Physical Therap. **46**:373 (Aug.) 1928.

15. Dreyfus, G. L., and Mayer, K.: Vier Jahre Malariabehandlung der multiplen Sklerose, Deutsche Ztschr. f. Nervenh. **111**:68, 1929.

16. Schmidt, W. H., and Weiss, B. P.: Fever Produced by Diathermy: Its Value in Multiple Sclerosis and Other Chronic Diseases, Physical Therap. **49**: 336 (Sept.) 1931.

17. Neymann, C. A., and Osborne, S. L.: The Treatment of Some Multiple Sclerotics by Electropyrexia, J. Nerv. & Ment. Dis. **79**:423 (April) 1934.

18. Weiss, B. P.: Further Observations on the Treatment of Multiple Sclerosis by Hyperpyrexia, M. Rec. **142**:489 (Dec. 4) 1935.

19. Wetherell, F.: Multiple Sclerosis: Cervicodorsal Sympathectomy as a Relief Measure; Report of a Case, J. A. M. A. **102**:1754 (May 26) 1934.

20. Royle, N. D.: The Surgical Treatment of Disseminated Sclerosis, M. J. Australia **1**:586 (May 13) 1933.

21. Koch, C. F., and de Savitsch, E.: Surgical Treatment of Disseminated Sclerosis by Sympathectomy and Ganglionectomy: Technique by the Anterior Approach, Brit. M. J. **1**:1254 (June 11) 1938.

of nicotinic acid without the difficulties, complications and dangers [22] incident to these methods.

Nicotinic acid when given in proper doses intravenously or intramuscularly produces vasodilatation in the skin of the face, neck, chest and extremities, as has been observed by Smith, Ruffin and Smith,[13] and subsequently by others [23] and in this series of cases. The readings of skin temperatures, as shown in tables 1 and 2, are the measurable objective evidence of vasodilatation and increased blood velocity in the skin. In view of the pathologic changes of multiple sclerosis centering in the spinal cord and brain, the goal of therapy is to alter or to arrest, if possible, the progress of an existing reversible pathologic process in these tissues.

The evidence presented in this paper that nicotinic acid produces vasodilatation and increased blood flow in the brain and spinal cord is based on the rise of cerebrospinal fluid pressure during the period of flushing of the skin, as shown in figures 1 and 2, and the photographic visualization of dilated vessels and increased capillary filling in the brain and spinal cord of the cat (figs. 3, 4, 5, 6 and 7). Elsberg and Hare,[24] in their studies on the amyl nitrite test for spinal subarachnoid block, showed that "amyl nitrite, given by inhalation, does produce a definite rise of intracranial pressure, which in an individual with an unobstructed spinal subarachnoid space can be easily measured by a spinal manometer." The rise of intracranial pressure after the inhalation of amyl nitrite is due to the expulsion of cerebrospinal fluid from the cranial cavity incident to an increased volume of the brain brought about by extensive dilatation of the cerebral vessels,[25] and in all probability of the spinal vessels as well.[24] The rise of cerebrospinal fluid pressure, as observed in cases 1 and 4, following the injection of nicotinic acid and coming on coincidentally with the subjective feeling of warmth and the objective appearance of flushing of the skin, is presumptive evidence of vasodilatation within the brain. The exposed brain and cervicothoracic portion of the cord of the cat showed vaso-

22. Hartman, F. W.: Lesions of the Brain Following Fever Therapy: Etiology and Pathogenesis, J. A. M. A. **109**:2116 (Dec. 25) 1937. Bennett.[12a] Collins.[12b]

23. (*a*) Spies, T. D.; Cooper, C., and Blankenhorn, M. A.: The Use of Nicotinic Acid in the Treatment of Pellagra, J. A. M. A. **110**:622 (Feb. 26) 1938. (*b*) Spies, T. D.; Bean, W. B., and Stone, R. E.: The Treatment of Subclinical and Classic Pellagra: Use of Nicotinic Acid, Nicotinic Acid Amide and Sodium Nicotinate, with Special Reference to the Vasodilator Action and the Effect on Mental Symptoms, ibid. **111**:584 (Aug. 13) 1938.

24. Elsberg, C. A., and Hare, C. C.: A New and Simplified Manometric Test for the Determination of Spinal Subarachnoid Block by Means of the Inhalation of Nitrite of Amyl, Bull. Neurol. Inst. New York **2**:347 (Nov.) 1932.

25. Sollmann, T.: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1936, pp. 479-481.

dilatation both visually and photographically after the intramuscular injection of nicotinic acid; this was most evident at the height of "pinking" of the cat's tongue and dental mucous membrane and constitutes the direct evidence of an increased blood flow in the brain and spinal cord produced by nicotinic acid.

The favorable results obtained in the cases reported may be due in part to the increased oxidation and nutrition of the brain and spinal cord brought about by the improved blood supply. Whether the salutary effect of nicotinic acid is due solely to its effect on the vasculature of the brain and spinal cord or to the possible additional role of nicotinic acid as a vitamin cannot be answered with any degree of certainty within the scope of this paper. Hopkins [26] placed nicotinic acid among the essential vitamins and assigned to it the important place of contributing to the complex structure of coenzymes part of the function of which consists of transferring hydrogen to oxygen. Thus nicotinic acid, in its biocatalytic action, may have some influence on the altered molecular state of the diseased nerve tissues in multiple sclerosis.

Although patients with pellagra [27] have responded favorably to the use of nicotinic acid as regards nervous and mental symptoms, it cannot be said that nicotinic acid alone was responsible for the effect on the nerve tissue. Spies, Cooper and Blankenhorn [23a] and Spies and Aring [28] have shown that vitamin B_1 deficiency is the factor in pellagra producing the peripheral neuritic phenomena. Lewy [29] stated that "the basic factor in most, if not all neuropathies, is a B avitaminosis." Nicotinic acid has been shown by Williams and Spies [30] to be part of the vitamin B complex. Deprivation of vitamin B_1 results in disturbance in the normal combustion of carbohydrates and the accumulation of pyruvic acid in the nervous system; both of these deviations from the normal produce significant physiologic and pathologic changes in nerve tissue, and replenishing of vitamin B_1 restores the ability of the nervous system to handle properly pyruvic acid and dextrose.[31]

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26. Hopkins, F. G.: Biological Thought and Chemical Thought, Lancet **1**:1201 (May 28) 1938.

27. Matthews, R. S.: Pellagra and Nicotinic Acid, J. A. M. A. **111**:1148 (Sept. 24) 1938. Spies, Bean and Stone.[23b]

28. Spies, T. D., and Aring, C. D.: The Effect of Vitamin B_1 on the Peripheral Neuritis of Pellagra, J. A. M. A. **110**:1081 (April 2) 1938.

29. Lewy, F. H.: Vitamin B Deficiency and Nervous Diseases, J. Nerv. & Ment. Dis. **89**:1 (Jan.) 1939.

30. Williams, R. R., and Spies, T. B.: Vitamin B_1 (Thiamin) and Its Use in Medicine, New York, The Macmillan Company, 1938, p. 131.

31. Lipschitz, M. A.; Potter, V. R., and Elvehjem, C. A.: The Metabolism of Pyruvic Acid in Vitamin B_1 Deficiency and in Inanition, J. Biol. Chem. **123**: 267 (March) 1938. Hopkins.[26]

Vitamin B_1 was used in conjunction with nicotinic acid in this series of cases, admittedly on an empiric basis. It was felt that whatever effect thiamin chloride may have on diseased nerve tissues, in the light of the foregoing presentation, its effect would be enhanced if it was active at the time vasodilation and improved blood supply were operative during the action of nicotinic acid.

Vitamin B_1 has been used by Stern [32] in treatment of a rather impressive list of conditions, among which is included multiple sclerosis. He administered the substance intraspinally and reported encouraging results. To my knowledge, there have been no reports in the literature regarding the use of nicotinic acid in treatment of multiple sclerosis.

In every case in this series in which nicotinic acid–vitamin B_1 therapy was halted for a period there was a return of incapacitating spasticity and incoordination; however, these symptoms were ameliorated within several days, or at most a fortnight, on restitution of treatment. The patients have been the severest judges concerning the relief they experience from the drugs, and in every case they have requested the return to their use after cessation of treatment for a short time.

An important question arises concerning the possible untoward effects of prolonged therapy and the large dose employed—as apparently is necessary in treatment of multiple sclerosis with nicotinic acid and vitamin B_1. It will be seen from the case reports that treatment has been in effect in case 1 since Feb. 15, 1938; in case 2 since March 3, 1938; in case 3 since March 1, 1938; in case 4 since the latter part of April 1938, and in case 5 since May 31, 1938. To date, untoward symptoms have not been encountered, and laboratory and electrocardiographic studies have not shown evidence of harmful effects.

To be sure, complete remissions have not been achieved by the use of nicotinic acid and vitamin B_1 in the cases reported. On the other hand, these cases were instances of advanced multiple sclerosis in which many forms of therapy had been used without appreciably arresting the progress of the disease; in 2 of the cases previous treatment had even aggravated the condition. Every patient noticed improvement in bodily movements and in walking: The patient in case 2 has been restored to her aptitude at the piano and has lost the annoying paraesthesias. Patient 4 is now able to stand and has overcome much of his extreme spasticity. Patient 5 is no longer bedridden and can move his legs, stand while assisted and use his arms, which were previously powerless, for purposes of dressing and eating. It is evident, therefore,

32. Stern, E. L.: The Intraspinal (Subarachnoid) Injection of Vitamin B_1 for the Relief of Intractable Pain, and for Inflammatory and Degenerative Diseases of the Central Nervous System, Am. J. Surg. **34**:495 (March) 1938.

that some improvement has resulted and, what is more significant, a stop has been called to the previous downward course in these cases.

What effect nicotinic acid–vitamin B_1 therapy may have in cases of early multiple sclerosis is still to be determined. Further investigation in such cases with both nicotinic acid and vitamin B_1, by use of other modes of administration and other doses, may yield more encouraging results and perhaps throw light on the many blindspots in knowledge of multiple sclerosis.

SUMMARY AND CONCLUSIONS

Five cases of advanced multiple sclerosis in which many forms of treatment had been used without appreciably halting the progress of the disease and in which the patients were treated with nicotinic acid and vitamin B_1 are reported.

Nicotinic acid produces vasodilatation not only of the skin but also of the brain and spinal cord.

Nicotinic acid and vitamin B_1 (thiamin chloride) may be given parenterally in considerable doses (nicotinic acid, 120 mg.; thiamin chloride, 33.2 mg.) for prolonged periods without apparent harmful effects.

Subjective and objective evidence of continued improvement has followed the parenteral use of nicotinic acid and vitamin B_1 in the cases of multiple sclerosis here reported.

1813 Delancey Street.

DISCUSSION

DR. J. C. YASKIN: Several thoughts occur in connection with a presentation of this sort. First, there are two diseases treatment of which is notoriously difficult to evaluate—Parkinson's disease and multiple sclerosis. Second, one knows that multiple sclerosis does have remissions, even when well advanced. Third, a great many patients with multiple sclerosis are easily influenced by suggestion; especially is this true of Dr. Moore's second patient, whom, I believe, I saw in the Orthopaedic Hospital. Fourth, some have been using vitamin B_1 in treatment of multiple sclerosis. As a matter of fact, the routine is, when possible, to give fever therapy with the hope that the disease is of virus origin and that some of the organisms may be killed. After this, quinine, liver, liver extract and wine are given when the patients can afford these agents, and I can assure Dr. Moore that a number of patients have shown considerable improvement when they have taken vitamin B_1 and liver. Last, although Dr. Moore had 1 patient under his observation only a few months, it is a year from the time of beginning the treatment. Although it is difficult to evaluate results, all in all, any one who can suggest something useful in the treatment of multiple sclerosis deserves a great deal of credit.

DR. MICHAEL SCOTT: I was much interested in Dr. Moore's experimental work with nicotinic acid. It was given to 1 patient at Temple University Hospital while on the operating table, and the exposed brain was observed. I did not see any change; however, that was in only 1 case, and only part of the temporal lobe was exposed.

DR. A. SILVERSTEIN: Dr. Moore's second patient, I think, went the rounds of every neurologist in Philadelphia. I saw him years ago; he had early signs of multiple sclerosis, but there was such a marked psychogenic overlay that the question of hysteria was considered. He was highly suggestible, and still is. He is now at the Philadelphia Home for Incurables, and is absolutely disabled. If one asks him how he is getting along, he says: "I feel fine, as long as I get that injection in me." On the day on which he does not receive an injection he feels sick. I have never seen the man stand. He still has severe spasticity; it all depends on what one means by making a person better. As far as he is concerned, he is disabled. Aside from the upper extremities, he is a cripple. I have seen 4 patients who have objected rather strenuously to this treatment.

DR. A. ORNSTEEN: Does Dr. Moore think that the response is due entirely to vasodilatation, to the exclusion of the replacement therapy of avitaminoses?

DR. MATTHEW T. MOORE: I realize fully that in bringing forth any new form of therapy of multiple sclerosis I am embarking on a stormy sea. However, any method or procedure that promises the slightest step forward in treatment of this particularly distressing disease will be of value.

As regards remissions in multiple sclerosis: Many patients do show remissions, but the recent article by Brown and Putnam (Remissions in Multiple Sclerosis, *Arch. Neurol. & Psychiat.* **41**:913 [May] 1939) showed clearly, I believe, the statistical evidence regarding remissions and the type of cases in which the remissions occur. They stated that in cases in which the lesions are small, producing such symptoms as diplopia, the probability of remissions is greater and the duration of the remission longer; in cases in which the lesions are large, producing paraplegias and advanced pathologic reflexes, the hope of remission is slight. The part played by suggestion I have, of course, taken into consideration. Any patient with a distressing disease, such as multiple sclerosis, in which the outlook is hopeless is always amenable to wishful thinking, to any hope that can be held out to him, and therefore is highly suggestible.

As I indicated by the lantern slide illustrations, nicotinic acid was used because I believe that if hyperemia similar to that in the skin could be brought about in the nervous system one could dispense with fever therapy and its deleterious effects on nerve tissue. Bennett, Hartman and others have shown that definite pathologic changes may occur in the brain and spinal cord as the result of fever therapy.

The statement that multiple sclerosis may be of virus origin is open to serious question. Pathologically, it is a degenerative disease from the start. As regards the end results in this series: I have been using this therapy for a year and three months in 2 cases and for a year in the remaining 3 cases; in the first 2 cases the improvement has been encouraging, despite the advanced stage of the disease in both.

In reply to Dr. Scott regarding the appearance of the brain after the injection of nicotinic acid: The "pinking" of the cerebral cortex is more or less determined by the dose of nicotinic acid. In man, unless 60 mg. of nicotinic acid is given as a minimum dose, there may not be any appreciable response.

None of the patients noted a favorable response in less than a week. The spasticity never decreased immediately. The diminution in spasticity was of a subjective character first. There was diminution in spasticity that could be observed objectively later; that this was not due to suggestion was simply shown in case 1 and in case 5, which I did not describe, that of a man who was absolutely bedridden and had not been able to move his body or lower limbs for six months. In two weeks he was able to move his toes, and in three months to undress himself. As regards the mental reaction of the second patient, mentioned by Dr. Silverstein, it is true he was suggestible. This man had the most advanced multiple sclerosis I have seen, with pronounced spasticity—so extreme that I was

afraid he had a tumor of the cord extending upward into the foramen magnum; however, careful studies eliminated this possibility. This patient was admitted with extreme spasticity and crossing of the legs. He can now uncross his legs voluntarily and is able to move in bed, which he formerly could not do.

As to Dr. Ornsteen's question regarding vasodilatation versus replacement therapy: I have used nicotinic acid on the basis of the effects of vasodilatation, increased oxidation and improved nutrition, which appear concomitantly with increased blood flow in the nervous system. As far as the replacement therapy is concerned, one knows that vitamin B_1 unquestionably plays a role in the degenerative neuropathies; for that reason, the two drugs were used simultaneously to obtain a complementary effect.

EFFECT OF THE RETICULOCYTOGENIC PRINCIPLE IN URINE IN THE TREATMENT OF PERNICIOUS ANEMIA

G. E. WAKERLIN, M.D., PH.D.
CHICAGO

Normal human urine contains a substance which, like the anti-pernicious anemia principle in liver, is reticulocytogenic for the pigeon, rat and guinea pig.[1] An extract of normal human urine prepared by a method basically that used for liver extracts has been found to be reticulocytogenic for the pigeon.[2] Decastello [3] reported that normal human urine administered intramuscularly or rectally is effective in the treatment of pernicious anemia, and McCann [4] found that kidney given by mouth is effective. These findings suggested the possible identity or similarity of the reticulocytogenic principle in urine and the hemopoietic principle in liver. In view of the nonspecificity of the pigeon, rat and guinea pig bioassay methods for the hemopoietic principle in liver, the possibility of urinary excretion of the principle was studied by administering the urine extract previously mentioned orally and intramuscularly to patients with pernicious anemia. A preliminary report of the effect of intramuscular injections of the urine extract in cases of pernicious anemia has been published.[5]

From the Department of Physiology, College of Medicine, University of Illinois, and the Department of Physiology and Pharmacology, University of Louisville School of Medicine.

1. Wakerlin, G. E., and Bruner, H. D.: Presence in Normal Human Urine of a Reticulocyte-Stimulating Principle for the Pigeon, Arch. Int. Med. **57**:1032 (May) 1936. Liener, G.: Ueber antianämisch wirksame Substanzen im Harn, Wien. klin. Wchnschr. **48**:559, 1935. Walters, O. S.: Reticulocytogenic Action of Pernicious Anemia Urine Extracts, Am. J. Physiol. **116**:158, 1936.

2. Wakerlin, G. E.; Bruner, H. D., and Kinsman, J. M.: A Modified Pigeon Method for the Bioassay of Anti-Pernicious Anemia Liver Extracts, J. Pharmacol. & Exper. Therap. **58**:1, 1936.

3. Decastello, A.: Ueber antianämisch wirksame Substanzen im Harn, Med. Klin. **31**:377, 1935.

4. McCann, W. S.: Effect of Kidney on Blood Regeneration in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **25**:255, 1928.

5. Wakerlin, G. E.: The Relation of the Reticulocytogenic Urine Principle to the Hemopoietic or Antipernicious Anemia Liver Principle, Am. J. Physiol. **119**:417, 1937.

METHOD

Urine extract was prepared by concentrating normal human urine to a small volume in vacuo at a temperature of 37 C., adding sufficient 95 per cent alcohol U. S. P. to give a concentration of 70 per cent, concentrating the resulting filtrate in vacuo to a small volume at 37 C., adding sufficient 100 per cent alcohol U. S. P. to give a concentration of 95 per cent and collecting and drying the precipitate. The precipitate derived from 600 cc. of urine and equivalent in reticulocytogenic effect on the the pigeon to the parenteral liver extract derived from 1,000 Gm. of liver was divided into two capsules, which were administered by mouth daily for ten days to each of a group of 3 patients with pernicious anemia. For intramuscular injection the precipitate was dissolved in sufficient physiologic solution of sodium chloride containing 0.5 per cent phenol to give a 1:20 ratio for the

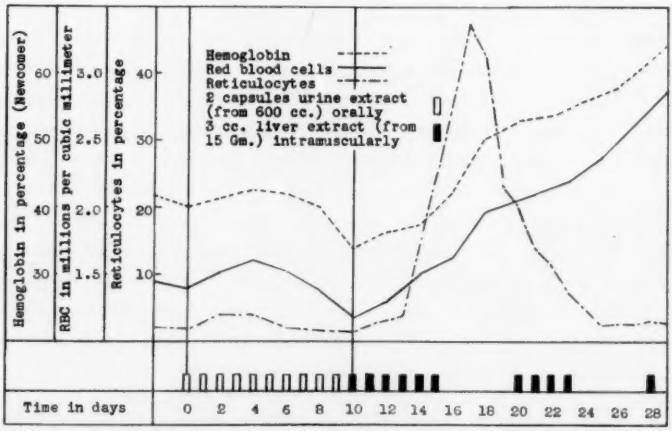
Hemoglobin in percentage (Newcomer)
RBC in millions per cubic millimeter
Reticulocytes in percentage
Hemoglobin
Red blood cells
Reticulocytes
2 capsules urine extract (from 600 cc.) orally
3 cc. liver extract (from 15 Gm.) intramuscularly
Time in days
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28

Chart 1.—Effect on hemoglobin, red blood cells and reticulocytes of oral administration of urine extract and intramuscular administration of liver extract.

volume of the extract and that of the original urine. The urine extract, equivalent in reticulocytogenic effect on the pigeon to a like quantity of two commercial liver extracts derived from 100 Gm. of liver, was administered intramuscularly in 3 cc. doses daily for ten days to each of a second group of 3 patients with pernicious anemia. Blood counts, except for daily reticulocyte determinations, were made at two to three day intervals before and during treatment with urine extract and during subsequent therapy with liver extract.

RESULTS

In the case of the first patient to receive urine extract by mouth the red blood cell count was 1,400,000 per cubic millimeter. The value for hemoglobin was 6.8 Gm. (Newcomer); the white blood cell count, 4,900 per cubic millimeter,

and the reticulocytes, 2.2 per cent at the beginning of treatment. The urine extract failed to produce any hematologic or clinical improvement over a ten day period, whereas the subsequent parenteral injection of liver extract resulted in a typical response (chart 1). The other 2 patients were likewise unaffected by the oral administration of urine extract, although subsequent treatment with parenterally administered liver extract was effective.

In the case of the first patient to receive urine extract intramuscularly the red blood cell count was 1,475,000 per cubic millimeter; the value for hemoglobin, 6.6 Gm. (Newcomer); the white blood cell count, 3,700 per cubic millimeter, and the reticulocytes, 0.2 per cent before treatment. The injections of urine extract were without hematologic or clinical effect during a ten day period. Subsequent treatment with parenterally administered liver extract produced the usual response (chart 2). The other 2 patients similarly showed no improvement with urine

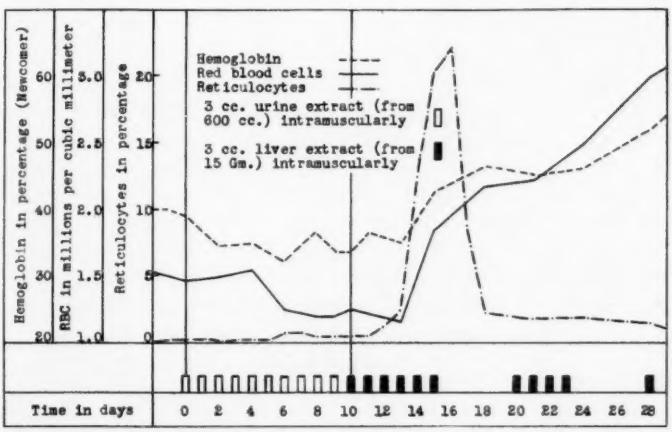
Hemoglobin in percentage (Newcomer)
RBC in millions per cubic millimeter
Reticulocytes in percentage
Hemoglobin
Red blood cells
Reticulocytes
3 cc. urine extract (from 600 cc.) intramuscularly
3 cc. liver extract (from 15 Gm.) intramuscularly
Time in days
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28

Chart 2.—Effect on hemoglobin, red blood cells and reticulocytes of intramuscular administration of urine extract and liver extract.

extract given parenterally, whereas liver extract parenterally administered produced a satisfactory response.

COMMENT

These results demonstrate conclusively that the anti-pernicious anemia principle in liver is not excreted in significant quantities, if at all, in normal human urine. In terms of reticulocytogenic effect on the pigeon, the amounts of urine extract administered were approximately ten times the therapeutically effective amounts for liver administered orally and intramuscularly; moreover, the urine equivalents used exceeded the amounts of urine reported effective by Decastello.[3] My previously reported observation on 1 patient, suggesting that urine extract was effective when given intramuscularly in a case of pernicious

anemia,[6] must be interpreted as due to a coincidental spontaneous remission. Jequier and Apsey [7] were unable to demonstrate the presence of the hepatic hemopoietic principle in normal human urine administered rectally to a patient with pernicious anemia.

The relation between the reticulocytogenic principle in urine and the hemopoietic principle in liver is obviously an open question. Possibly the urinary principle is a decomposition product or a "building stone" of the hepatic principle. The presence of the urinary reticulocytogenic principle or one indistinguishable from it in the urine of untreated patients with pernicious anemia [8] does not necessarily speak against the former possibility and is compatible with the latter. The principle in kidney which is effective by oral administration in cases of pernicious anemia may conceivably be an intermediary between the urinary principle and the hepatic principle. Thus, two extracts of kidney [9] prepared by methods identical with those employed in making liver extracts for parenteral use proved to have a reticulocytogenic potency for the pigeon equal to that of liver extracts but were completely ineffective when given intramuscularly to 2 patients with pernicious anemia.[5] Dakin, Ungley and West [10] have reported similar findings. In other words, although all three principles are reticulocytogenic for the pigeon, rat and guinea pig, in the treatment of pernicious anemia the hepatic principle is effective orally and parenterally, the renal principle is effective orally but not parenterally, and the urinary principle is effective by neither route. Obviously more work must be done before the interrelations of these three principles, if any, are clarified.

CONCLUSIONS

1. The principle in normal human urine which is reticulocytogenic for the pigeon, rat and guinea pig is not effective orally or intramuscularly in the treatment of pernicious anemia.

2. The anti–pernicious anemia principle in liver is not excreted in demonstrable quantities, if at all, in normal human urine.

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6. Wakerlin, G. E.: Presence of Anti-Pernicious Anemia Principle in Normal Human Urine, Proc. Soc. Exper. Biol. & Med. **32**:1607, 1935.

7. Jequier, E., and Apsey, G. R. M.: The Anti-Pernicious Principle: Some Experiments with Urine, Brit. M. J. **2**:934, 1938.

8. Wakerlin, G. E.: Unpublished data. Jequier and Apsey.[7]

9. The kidney extracts were supplied by the Lederle Laboratories, Inc., Pearl River, N. Y. (Dr. Guy W. Clark), and the Abbott Laboratories, North Chicago (Dr. J. F. Biehn).

10. Dakin, H. D.; Ungley, C. C., and West, R.: Further Observations on the Chemical Nature of a Hematopoietic Substance Occurring in Liver, J. Biol. Chem. **115**:771, 1936.

3. The principle in kidney which is effective by mouth in pernicious anemia is reticulocytogenic for the pigeon but is ineffective when administered intramuscularly to patients with pernicious anemia.

4. A clarification of the interrelations of these hepatic, renal and urinary principles should enhance physicians' knowledge of the metabolism of the anti–pernicious anemia principle in liver.

Drs. Joseph Liebman and H. D. Bruner assisted in certain phases of this work. Drs. R. W. Keeton and J. W. Moore made some of the patients available for study.

DISSEMINATED LUPUS ERYTHEMATOSUS: A CUTANEOUS MANIFESTATION OF A SYSTEMIC DISEASE (LIBMAN-SACKS)

REPORT OF A CASE

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AND
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NEW YORK

Disseminated lupus erythematosus is a distinctive cutaneous eruption forming part of a systemic disorder that usually includes also characteristic clinical and anatomic evidences of visceral damage. It is now believed that this disorder may occur without its cutaneous manifestation. There exists a considerable body of literature, chiefly dermatologic, in which the clinical aspects of the disease have been well depicted. Though this literature extends back almost seventy years, it is only within the last fifteen years that the present concept of the disease has been evolved and that the visceral lesions observable in most cases have been accurately described.

The chronic forms of lupus erythematosus, whose relation to the disease under discussion has not yet been fully evaluated, have been known since the early part of the last century as localized cutaneous conditions. However, on the basis of the original observations of Kaposi,[1] it has become apparent that with other forms of lupus erythematosus (particularly the acute and subacute disseminated types) there is clinical evidence of an accompanying systemic disease. In some cases the condition pursues an acute, febrile, rapidly progressive course from the onset, soon terminating fatally. In others, the course is less rapid and commonly shows remissions of variable extent. In general, however, the concept has been evolved of a consistent clinical syndrome which permits of the diagnosis, especially in the presence of the cutaneous eruption. Among the more common clinical features, which may be observed in various combinations, are: fever, prostration, loss of weight and weakness; changes in the blood (leukopenia, anemia, thrombopenia) and in the urine (albumin, casts, blood); hemorrhagic phenomena (extensive purpura, petechiae with or without pale centers, bleeding

From the Laboratory Division and Medical Service, Hospital for Joint Diseases.

1. Kaposi, M.: Neue Beiträge zur Kenntnis des Lupus erythematosus, Arch. f. Dermat. u. Syph. **4**:36, 1872.

from mucous membranes); evidence of serous membrane involvement (pleuritis, pericarditis, ascites); severe articular involvement, lymphadenopathy, enlargement of the spleen and abdominal complaints. These different symptoms may vary greatly in severity; any of them may be lacking in an individual case.

The causation of the disease remains unknown. In the past, chiefly tuberculous and streptococcic infections have been incriminated. In our opinion these have now been excluded as specific causes of the disease. There is a tendency at present to regard the disease as a peculiar response, in a constitutionally predisposed person, to a variety of harmful agents. However, the possibility of an as yet undiscovered specific cause cannot be denied.

The evolution of the present concept of this remarkable disease has coincided with the recent advances resulting from detailed gross and microscopic examination of the internal organs; such examinations were seldom made in the earlier cases. The foundation for the present understanding of the disease is deeply rooted in the observations of Libman [2] on a peculiar type of endocarditis associated with a unique clinical syndrome. The latter, in retrospect, is a pattern of that which may be found in cases of disseminated lupus erythematosus. Indeed, Libman-Sacks disease (as the aforementioned syndrome has come to be called) not infrequently presents, as one of its clinical manifestations, the cutaneous eruption of disseminated lupus erythematosus.

The concept has been further developed by the studies of Baehr [3] and of Gross [4] on Libman-Sacks disease, by those of Baehr, Klemperer and Schifrin [5] on disseminated lupus erythematosus and by the later studies of Gross [6] on the relation between Libman-Sacks disease and disseminated lupus erythematosus.

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2. (*a*) Libman, E.: Some General Considerations Concerning Affections of the Heart Valves, M. Clin. North America **1**:573 1917; (*b*) Characterization of Various Forms of Endocarditis, Tr. A. Am. Physicians **37**:233, 1922; J. A. M. A. **80**:813 (March 24) 1923. (*c*) Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Tr. A. Am. Physicians **38**:46, 1923; Arch. Int. Med. **33**:701 (June) 1924.

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4. Gross, L.: The Heart in Atypical Verrucous Endocarditis (Libman-Sacks), in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, p. 527.

5. Baehr, G.; Klemperer, P., and Schifrin, A.: A Diffuse Disease of the Peripheral Circulation Usually Associated with Lupus Erythematosus and Endocarditis, Tr. A. Am. Physicians **50**:139, 1935.

6. Gross, L.: Unpublished data; cited by Friedberg, C. K.; Gross, L., and Wallach, K.: Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, Arch. Int. Med. **58**:662 (Oct.) 1936; cited by Libman.[14]

We are presenting a detailed report of a case of disseminated lupus erythematosus in which the diagnosis was made clinically and verified by postmortem examination.[7] Of great interest is the presence of lesions of a distinctive nature in the lymph nodes and the spleen. Their occurrence in the disease has been noted by a few observers, but thus far they have apparently not been considered sufficiently important to warrant a detailed description.

Our case is apparently the first reported in which the characteristic microscopic changes described by Baehr, Klemperer and Schifrin [5] have been demonstrated in a male patient. A notable feature of the disease is its striking predilection for females; indeed, doubt has been expressed as to whether it actually occurs in men. Nevertheless, even if cases without visceral complications are omitted, there remain a number of reports of cases of acute and subacute disseminated lupus erythematosus in male patients, with such characteristic features as a febrile course, anemia and leukopenia, evidence of renal damage and frequently a fatal outcome.[8] It is true that these reports are open to criticism because of incomplete clinical data and uncertainty about the pathologic changes. However, in the light of the case to be presented it is probable that the cases reported actually did present valid examples of the disease.

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7. Ginzler, A., and Fox, T. T.: Disseminated Lupus Erythematosus in a Youth, with Some Unusual Findings, Arch. Path. **26**:916 (Oct.) 1938.

8. (*a*) Hardaway, W. A.: A Case of Lupus Erythematosus Presenting Unusual Complications, J. Cutan. Dis. **7**:447, 1889. (*b*) Pernet, G.: Le lupus érythémateux aigu d'emblée, Thesis, Paris, no. 20, 1908. (*c*) Kraus, A., and Bohac, C.: Bericht über acht Fälle von Lupus erythematodes acutus, Arch. f. Dermat. u. Syph. **93**:117, 1908. (*d*) Brown, G. A.: A Case of Acute Erythematous Lupus, New York M. J. **106**:931, 1917. (*e*) Ehrmann, S., and Falkenstein, F.: Ueber Lupus Erythematodes, Arch. f. Dermat. u. Syph. **141**:408, 1922. (*f*) Goeckerman, W. H.: Lupus Erythematosus as a Systemic Disease, J. A. M. A. **80**:542 (Feb. 24) 1923. (*g*) Gibson, R.: Fatal Case of Lupus Erythematosus with Post-Mortem, Brit. J. Dermat. **37**:232, 1925. (*h*) Stokes, J. H.: Diagnosis of Disseminate Erythematous Lupus, M. Clin. North America **10**:290, 1926. (*i*) Clarke, F. B., and Warnock, A. W.: Lupus Erythematosus Acutus Disseminatus, California & West. Med. **24**: 354, 1926. (*j*) Brown, C. F., and Bi, Y. W.: Lupus Erythematosus: Case Report, China M. J. **42**:775, 1928. (*k*) Madden, J. F.: Acute Disseminated Lupus Erythematosus, Arch. Dermat. & Syph. **25**:854 (May) 1932. (*l*) Lyon, J. M.: Acute Lupus Erythematosus, Am. J. Dis. Child. **45**:572 (March) 1933. (*m*) Roxburgh, A. C.: Acute Disseminated Lupus Erythematosus: Five Fatal Cases, Brit. J. Dermat. **45**:95, 1933. (*n*) Garfield, W. T.; Steele, C. W., and Houghton, J. D.: Lupus Erythematosus Disseminatus Acutus Haemorrhagicus, Arch. Dermat. & Syph. **30**:772 (Dec.) 1934. (*o*) Snapper, I.: Kidney Trouble in Acute Lupus Erythematosus, in Berglund, H., and Medes, G.: The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935, p. 433. (*p*) Rose, E., and Goldberg, L. C.: The Visceral Lesions of Acute Disseminated Lupus Erythematosus, M. Clin. North America **19**:333, 1935.

REPORT OF CASE

History.—H. M., a 17 year old youth of Anglo-Scotch origin, with no history of sunburn or abnormal sensitivity to light, was entirely well until Oct. 12, 1937, when he noted pain in the right ankle and thought he had sprained it playing baseball. There was no swelling or redness. The next day he experienced a sensation of feverishness and had about half a dozen chills, each lasting five to ten minutes. On successive days he then suffered from aching of both shoulders, swelling and severe pain in both elbow joints, and then swelling and tenderness of the metatarsophalangeal and proximal interphalangeal joints. At this time he was seen by a physician and thought to have rheumatic fever. He felt very weak and was put to bed. After three weeks he felt well enough to go to school, but one week later he collapsed and returned to bed. From this time on (about the middle of November), his temperature varied between 101 and 105 F. During the first week in December a roentgenogram of his teeth revealed abscesses, and two teeth were extracted. Immediately afterward there was a rise in temperature, with chills and sweating. The patient became confined to bed and lost weight and strength continuously. During the last two weeks in December there were generalized aching, tenderness and wasting of muscles, with severe contractures of the elbows and knees. In the last week the knees became very painful, though not red or swollen, and there appeared for the first time a symmetric butterfly-shaped erythematous eruption of the face. The patient was admitted to the Hospital for Joint Diseases Jan. 1, 1938, to the medical service of Dr. Albert A. Epstein, who supplied the clinical data reported here.

Examination.—On admission the boy was subacutely ill and very weak and had evidently lost much weight. He was of slender build but entirely masculine in features.

The face presented a symmetric macular erythematous eruption, associated with some scaling, over the flush area. The redness and scaling extended over the eyebrows, and there were slight scaling lesions of the lobes of the ears. The palmar surfaces of the thumbs presented irregular erythematous patches with slight purplish discoloration and rather firm adherent scales in the centers. Similar but smaller lesions were observed on the other finger tips. There were erythematous patches on the knees, and the elbows showed scaling. The mouth presented a marked stomatitis; the mucosa was reddened and covered by numerous small adherent whitish plaques with surrounding reddened zones.

Examination of the heart, lungs and abdomen revealed nothing noteworthy. The blood pressure was 115 systolic and 65 diastolic. The genitalia were normal. Rectal examination revealed a small anal ulcer. The extremities showed evidence of considerable muscular atrophy, and there was marked limitation of extension of the elbows and knees due to the extreme tenderness of the muscles, spasticity and capsular contractures.

Laboratory Data.—The urine contained albumin (2 plus), a moderate number of epithelial cells, leukocytes, occasional erythrocytes, and cellular casts.

The blood contained 10.6 Gm. of hemoglobin per hundred cubic centimeters (70 per cent) and 3,680,000 erythrocytes and 4,600 leukocytes per cubic millimeter; a smear showed 72 per cent segmented and 5 per cent nonsegmented neutrophilic leukocytes, 21 per cent lymphocytes, and 2 per cent monocytes.

The blood culture and usual agglutination tests of the serum were negative. The agglutination titer of the serum for a strain of hemolytic streptococcus was 1:640. The Kahn reaction was 2 plus; the Wassermann reaction, negative.

The electrocardiogram showed a low T wave in leads I and II and a diphasic T wave in lead IV, which was interpreted as indicating myocardial damage.

Course.—During the patient's stay in the hospital his temperature was generally between 100 and 102 F. It was higher in the evening than in the morning, usually varying about 2 degrees daily. Occasionally it went as low as 98 F. and as high as 103 F.; terminally it rose to 105 F. The urine always contained albumin, varying from a trace to 4 plus, with a tendency toward the larger amounts in the latter stages of the illness. Erythrocytes, leukocytes and granular and hyaline casts were constantly present in the urinary sediment. Repeated blood cultures were sterile. The Frei test gave negative results. The intradermal tuberculin test elicited negative reactions with dilutions of 1:10,000,000 to 1:1,000. The Wassermann reactions varied from negative to 2 plus; the Kahn, from 1 to 4 plus. The positive reactions were regarded as nonspecific. The platelet count at first was 196,000 per cubic millimeter, but later dropped to 92,000. Leukopenia was constant, the leukocyte count varying from 4,100 to 5,800.

On the eighth day after admission the patient experienced a clonic seizure, involving the face and extremities and accompanied by a feeling of dizziness, which lasted for twelve minutes and was followed by nausea and vomiting.

While tachycardia had been practically always present, no murmurs had been heard. Two days after the clonic seizure, a distant to and fro pericardial rub was heard for the first time, about 2.5 cm. inside the left nipple line. An electrocardiogram at this time showed an inverted T wave in leads II and III and a diphasic or upright T wave in lead IV. It was interpreted as indicative of myocardial damage and consistent with a diagnosis of pericarditis.

Four days later the patient had mild diarrhea and complained of abdominal pain. At about this time there was first noted a moderate generalized lymphadenopathy, most marked in the cervical and inguinal nodes but also involving the axillary and epitrochlear nodes. On January 16, two tender erythematous nodules appeared in the right anterior axillary line just above the nipple; they were removed for examination on January 20. Cultures of the excised material remained sterile on all mediums. On histologic examination the nodules proved to be lymph nodes. In addition to follicular hyperplasia and some swelling of the cells of the pulp and the follicular reticulum, there were several areas of cellular necrobiosis involving the pulp adjacent to marginal sinuses and the contiguous capsular tissue. Many of the cells in the affected areas showed swelling and a granular or fibrinous degeneration, with nuclear pyknosis and karyorrhexis. Other cells were completely disintegrated. Silver stains showed relatively little damage to the reticulum fibers in the necrotic areas. The abutting lymphoid tissue showed little monocytic or other reactive inflammation. There was a moderate cellular infiltration of the capsular tissue, predominantly lymphocytic, with a moderate number of plasma cells and a few eosinophils. Staining for bacteria did not reveal any tubercle or other bacilli.

These changes at first suggested the possibility of tularemia, but repeated agglutination tests for it were negative. At this time the histologic changes in the lymph nodes were compared with those recorded in our files for a case of disseminated lupus erythematosus, and their essential similarity was demonstrated. Material from a second group of nodes was injected into guinea pigs, with negative results.

Toward the end of January the facial eruption began to fade, and moderate hypertension (140/90) developed, which was considered all the more significant in view of the marked debility present. Later, petechiae (not white centered) appeared on the finger tips. Abdominal pain recurred. Biopsy of the calf muscle on February 15 revealed no evidence of dermatomyositis or periarteritis nodosa. Meanwhile, the general condition pursued a progressively downhill course. The tachycardia persisted, though after a time the pericardial rub was no longer heard.

Endocardial murmurs were never elicited. The facial eruption continued to fade and finally disappeared, a few weeks before death, with no residual marks or evidence of atrophy. The debility, emaciation, muscle tenderness and joint contractures became steadily worse. Terminally there occurred several convulsive seizures marked by loss of consciousness and clonic movements of the face and right arm. The day before death a bilateral wrist drop developed. Death occurred on March 3, a little less than five months after the onset of the first symptoms.

Gross Observations at Autopsy.—Postmortem examination was performed six hours after death. There were marked atrophy of the fatty tissue and the muscles throughout the body, and striking edema of the connective tissues. The lungs showed congestion and edema and an extensive bronchopneumonia. Over the lower lobe of the left lung, away from any area of pneumonia, there was a small patch of fibrinous pleuritis. There was no evidence of recent, old or healed tuberculosis in either the parenchyma or the tracheobronchial lymph nodes. The heart was

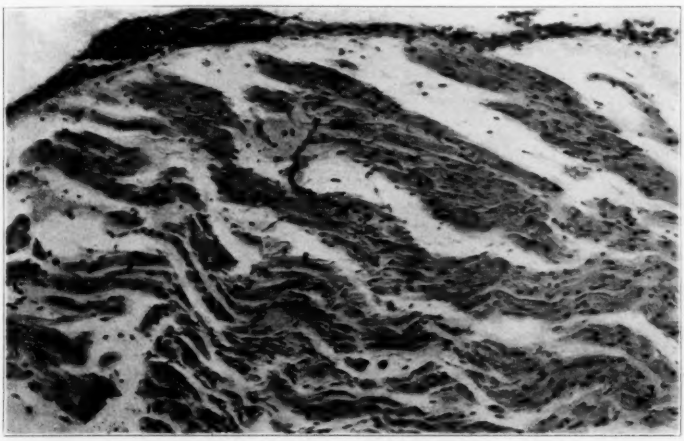

Fig. 1.—Endocardial lesion of right ventricle (hematoxylin and eosin stain; medium power). The section shows an adherent mass of granular material containing nuclei; there are swelling and proliferation of adjacent endothelial cells.

markedly hypertrophied, weighing 490 Gm., with adherent parietal pericardium. The pericardial leaflets were much thickened and completely adherent over their entire extent. No macroscopic valvular, pocket or mural endocardial lesions could be demonstrated. The liver showed only slight fatty change. The spleen was moderately enlarged, weighing 240 Gm.; the sections were firm and congested; in addition to follicles of normal prominence, there were numerous scattered pinhead-sized and somewhat larger yellowish areas. The macroscopic appearance resembled that of a tuberculous spleen. The splenic vessels showed no changes. The kidneys showed only a small area of recent infarction in the right kidney, with a thrombosed artery at its apex. The lymph nodes throughout the body—mediastinal, pancreatic, portal, mesenteric, renal and para-aortic—were enlarged, some to a marked degree. On section, the majority showed numerous pinhead-sized and larger opaque yellowish areas which might well have been mistaken for tuberculous lesions. Examination of the articular cartilages and synovial tissues of the right knee, which was one of the last joints clinically involved, showed no

gross alterations. Unfortunately, limitation of permission for autopsy precluded examination of the other joints or of the brain, or removal of sections of the affected skin for histologic examination.

Microscopic Observations at Autopsy.—Heart: Despite the absence of macroscopic vegetations, histologic study revealed numerous microscopic lesions of the mitral and tricuspid leaflets and the mural endocardium, which were apparently the result of toxic damage to the endothelium. The younger lesions were marked by swelling, proliferation and, frequently, degenerative changes of the lining endothelial cells and slight swelling of the subendothelial tissues. The subendothelial tissue in some areas contained an increased number of cells, many showing nuclear pyknosis and cytoplasmic degeneration, and infiltration by mononuclear cells, young fibroblasts and a few lymphocytes. In one or two there were a few

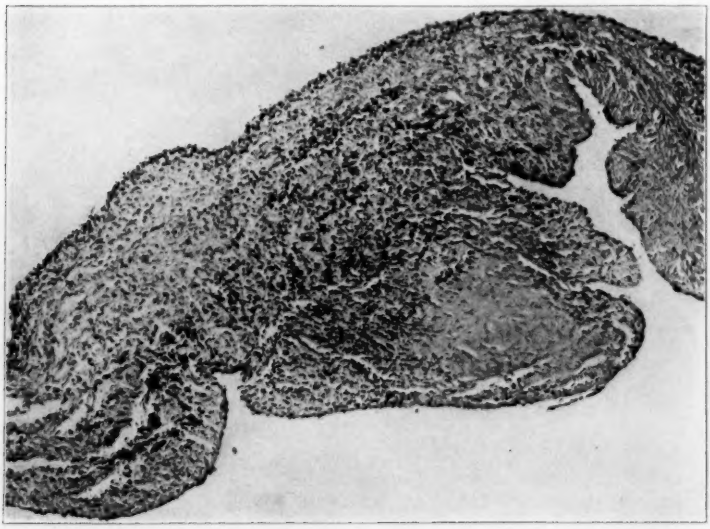

Fig. 2.—Inflammatory lesion of tricuspid valve.

polymorphonuclear leukocytes. In such areas the lining endothelial cells were enlarged and basophilic and contained dark-staining nuclei. One section showed areas of endothelial swelling close to the pocket of the tricuspid leaflet, with adherent masses of pink-staining granular material containing mononuclear cells and numerous dark-staining round or oval nuclei, some of which were pyknotic. The leaflet itself showed a diffuse inflammatory cellular infiltration consisting of polymorphonuclear leukocytes, monocytes, fibroblasts and a few lymphocytes. Many of the cells showed nuclear pyknosis and were difficult to identify. The lining endothelial cells of the valve showed distinct swelling and proliferation. The valve ring was entirely normal. Bacterial stains of the endocardial lesions gave uniformly negative results.

Other than the hypertrophy noted grossly, the myocardium showed no significant changes. Myocardial vascular lesions, Aschoff bodies, Bracht-Waechter lesions and myocardial degenerative changes were not observed. The coronary arteries showed nothing remarkable.

There was pronounced thickening of the pericardium due to a subacute and chronic organizing pericarditis. Some areas were already fibrous and avascular. However, most of the pericardium consisted of inflamed vascular granulation tissue showing considerable fibroblastic proliferation, numerous granulation capillaries with swollen endothelial cells, large numbers of plasma cells, peculiar mononuclear and multinucleated cells and, in places, lymphocytes and polymorphonuclear leukocytes. The latter were especially numerous about areas of fibrinous necrosis. In some places there were large clefts lined by swollen basophilic mesothelial cells.

Kidneys: While many of the glomeruli appeared normal, the majority showed distinct changes in some portions, with other portions unaffected. Most of the glomeruli involved were grouped along an interlobular artery. A striking change was an irregular thickening of the basement membrane of many of the capillary

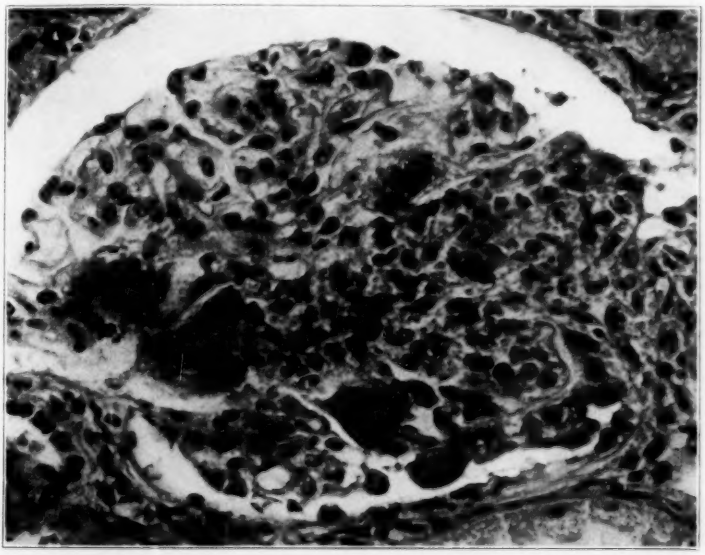

Fig. 3.—Glomerular lesion (hematoxylin and eosin stain; high power). The section shows extensive degenerative and proliferative changes described in the text (see also figs. 4 and 5).

loops, giving rise to the "wire-loop" lesion of Baehr, Klemperer and Schifrin.[5] Staining of these lesions for amyloid and lipoid gave negative results. Many capillary loops, especially those with thickened walls, contained smooth, pink-staining globules partially or completely obstructing the lumen.

Perhaps even more conspicuous were changes involving the endothelial cells and, to a lesser extent, the visceral epithelial cells of the glomerular tufts. The latter, in places, were considerably swollen. Many revealed a basophilic granular degeneration of the cytoplasm. Their nuclei were sometimes enlarged, bizarrely shaped and hyperchromatic, and sometimes pyknotic. Here and there the tuft was adherent to the glomerular capsule. The endothelial cells showed pronounced

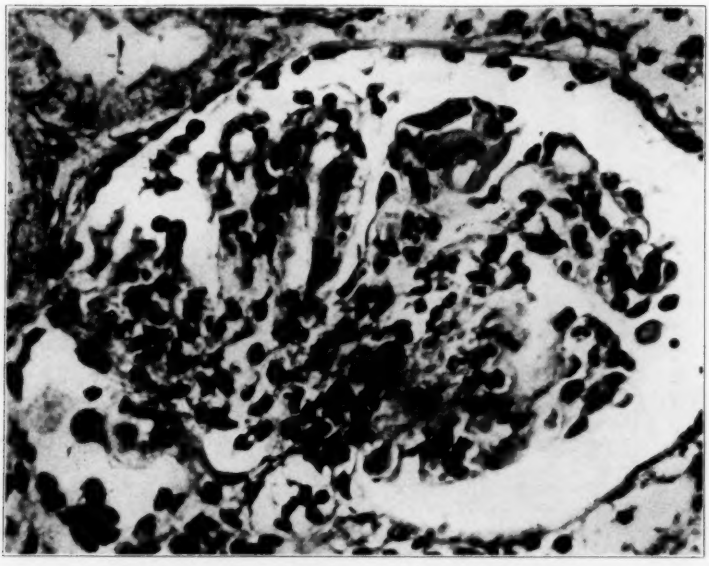

Fig. 4.—Glomerular lesion. (See legend for figure 3.)

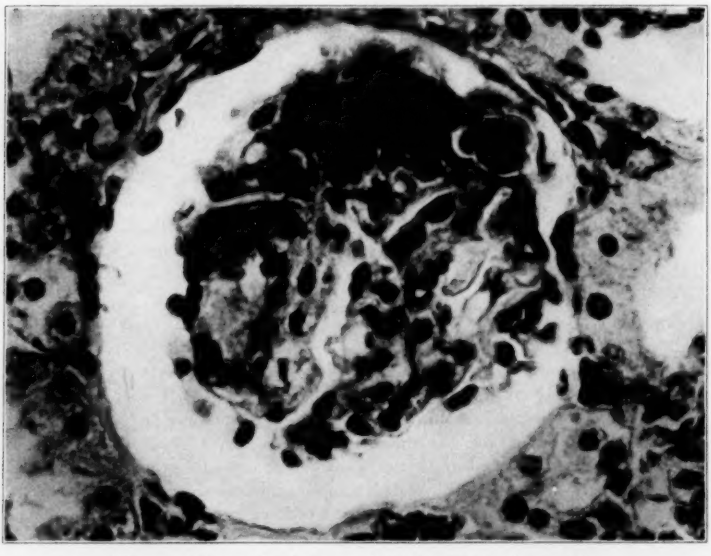

Fig. 5.—Glomerular lesion. (See legend for figure 3.)

swelling and proliferation, completely filling some of the loops and contributing to a distinct increase in cellularity of many of the glomeruli. The cells showed occasional hyaline droplet degeneration, but much more severe and extensive were pinkish violet-staining granular degeneration and necrosis of these cells, associated with nuclear pyknosis and karyorrhexis. The changes were often most pronounced at the hilus of the glomerulus. Study led to the conclusion that the formation of the glomerular thrombi was related to the endothelial degenerative changes. This was especially notable in sections stained by the aniline methyl violet method of Weigert; in these both the degenerative cytoplasmic granules and the capillary thrombi (though not the thickened capillary wall) took the violet stain with apparent transitions between.

The tubular epithelium showed moderate cloudy swelling and occasional hyaline droplet degeneration. Many tubules contained granular and hyaline casts. No

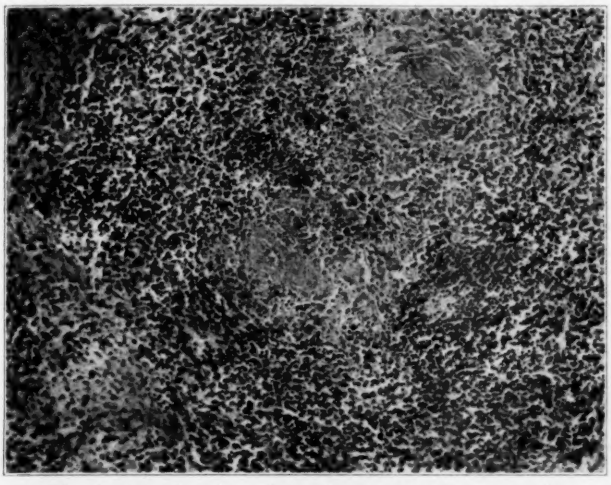

Fig. 6.—Lymph node. The section shows foci of necrosis.

unusual alterations were observed in the arterioles, arteries and veins. The infarcted area, noted grossly, showed complete necrosis of the tissue with an acute reactive inflammation. A recently thrombosed artery was present at the apex of the infarct, the thrombus most probably originating locally from endothelial damage.

Lymph Nodes: Some lymph nodes showed merely edema, sinus hyperplasia and an inflammatory reaction manifested by the presence of many histiocytic cells and a few plasma and polymorphonuclear cells. Most of the nodes, however, contained numerous areas of necrobiosis, apparently in different stages of development. The earliest consisted of foci of cellular necrobiosis with virtually no reactive inflammation. These progressed to larger areas of necrosis with complete cell degeneration and disintegration and nuclear pyknosis and karyorrhexis. Nuclear particles were spread throughout the surrounding pulp, which showed marked histiocytic proliferation. Silver stains revealed relatively little damage to the reticulum fibers in the affected areas. In many of these areas, some of the affected cells underwent a

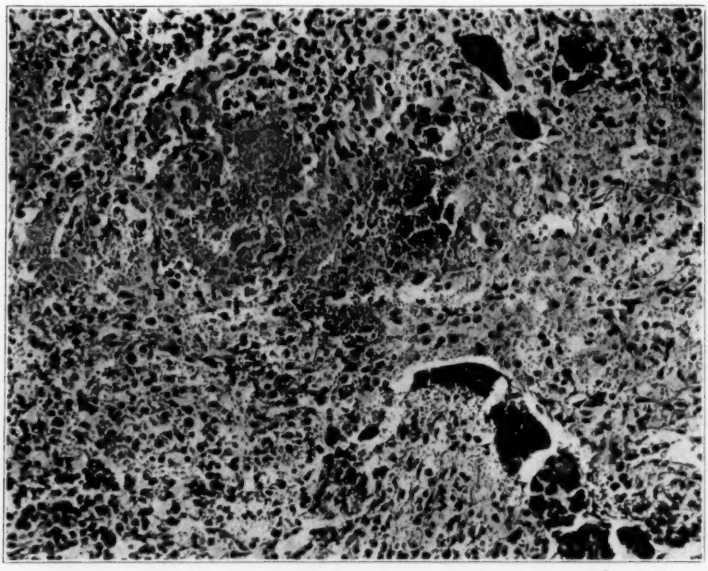

Fig. 7.—Lymph node. The section shows a focal area of necrosis with hematoxylin-staining bodies.

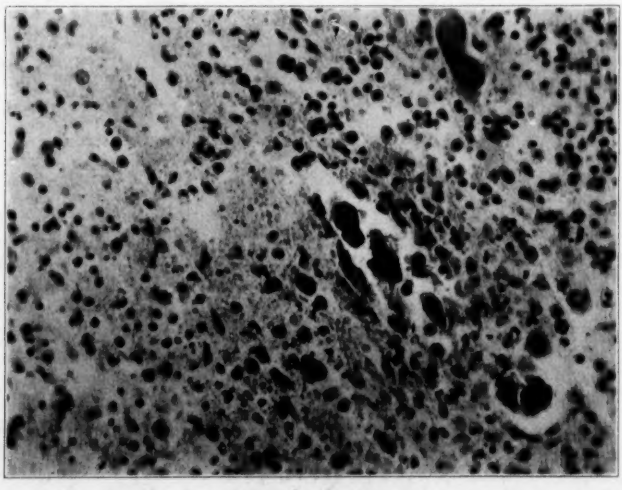

Fig. 8.—Lymph node. The section shows the formation of hematoxylin-staining bodies by coalescence of degenerating cells.

Fig. 9.—Spleen. The section shows a large area of periarterial necrosis of malpighian follicle.

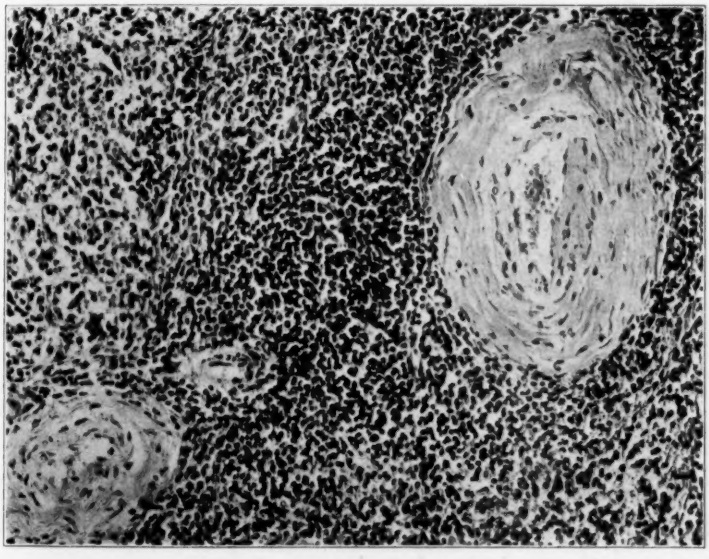

Fig. 10.—Spleen. The section shows intimal thickening and marked periarterial fibrosis.

pinkish blue granular degeneration of the cytoplasm with nuclear pyknosis, apparently coalescing to form striking bluish violet-staining masses, resembling calcium, in the hematoxylin-eosin sections. Von Kossa stains, however, revealed no calcium. The surrounding lymphoid tissue showed swelling of the reticulum cells and pronounced swelling and proliferation of the sinus endothelium. In some places there was conspicuous phagocytosis of nuclear particles and of erythrocytes. A small amount of iron pigment was present. In no way did these lesions resemble those of tuberculosis, nor did specific stains reveal any tubercle or other bacilli. Some of the lymph nodes showed strands of fibrosis.

Spleen: The most conspicuous change was the presence of numerous areas of necrobiosis of the lymphoid tissue about the follicular arteries. While they closely resembled the lesions in the lymph nodes, these areas in the spleen all represent a similar stage of progression. They consisted essentially of areas of cellular necrosis

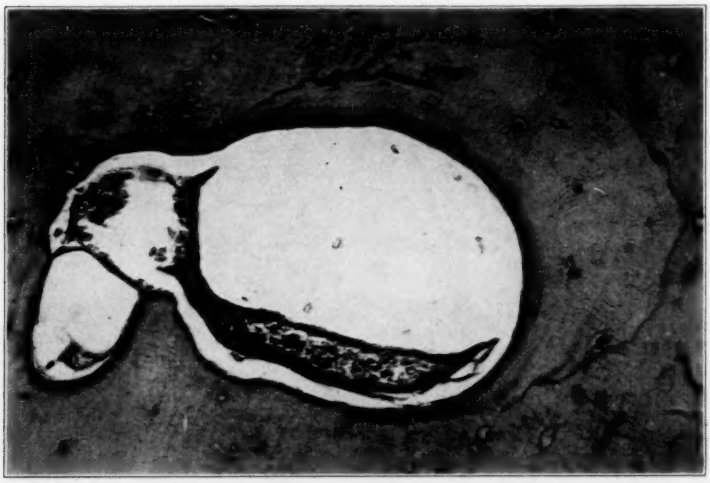

Fig. 11.—Vascular lesion in cortex of rib. The section shows marked thickening of the capillary wall. There is "creeping" replacement of adjacent osseous tissue.

with nuclear pyknosis and karyorrhexis and little damage to the reticulum fibers. There was no noteworthy reactive inflammation except for the occasional presence of mononuclear histiocytic cells. The arteries of the follicle showed conspicuous adventitial fibrosis and, in places, intimal proliferation.

The pulp revealed marked engorgement of the intersinusoidal cords, most of the sinuses being empty of blood and the sinus endothelium conspicuous. The red pulp was not involved in the areas of necrosis. There was no significant inflammatory reaction. A fair amount of intracellular iron pigment could be demonstrated.

Lungs: Sections showed edema and an extensive patchy bronchopneumonia, not unusual in character. In one section there was an area of swelling, proliferation, and marked degeneration of the lining mesothelial cells and pleural connective tissue. The pleura was covered by a thin film of fibrin. Other than these, the lungs showed no noteworthy changes. In particular, no vascular alterations were noted.

Osseous System: Sections of red marrow showed definite hypoplasia of the blood-forming elements, though all were present in normal proportions. There were pronounced capillary engorgement and edema of the fatty marrow, such as are often observed in debilitating diseases. The marrow revealed no vascular alterations or areas of necrosis. In the bone cortices, however, especially of the ribs, many of the capillaries presented a very striking thickening of their walls.

Knee: Sections of the synovial tissues and articular cartilages of the right knee showed surprisingly little change. In places there was slight hyperplasia of the synovial lining cells and at one point a small bit of fibrin covered the surface. The sublining synovial tissues showed no inflammatory or vascular alterations.

Blood Vessels: In addition to the abnormalities noted heretofore there were distinct dilatation and thickening of the capillaries throughout the connective tissues of the body. Furthermore, a number of small vessels showed partial thrombosis and organization.

Other Tissues: Changes elsewhere were not conspicuous. A section of skin taken from an erythematous area of the thumb showed marked capillary dilatation but no thrombosis or hemorrhage. There were no significant dermal or epidermal changes. Unfortunately, limitation of the permission for autopsy prohibited removal of other affected areas of skin. Sections of voluntary muscle showed atrophy, irregular degenerative changes of the muscle fibers and occasional mild interstitial inflammation. The liver, pancreas, adrenals, bladder, seminal vesicles and testes showed no significant changes.

COMMENT ON CASE

Aside from the unusual occurrence of the disease in a male subject, a review of the clinical data in this case elicits a number of points of interest which are important because of their not infrequent occurrence and consequent significance in regard to disseminated lupus erythematosus: (1) onset with polyarthralgia, (2) exacerbation of symptoms following removal of focus of infection, (3) appearance of a butterfly-shaped erythematous facial eruption two months after the onset of symptoms, (4) febrile course with clinical evidence of pericarditis (accompanied by electrocardiographic changes), renal damage, depression of bone marrow function (leukopenia, anemia, thrombopenia) and nontuberculous lymphadenopathy, (5) tachycardia, (6) elevation of blood pressure, (7) negative tuberculin and Frei tests, repeatedly negative blood cultures and negative serologic tests for typhoid and paratyphoid fevers, undulant fever and tularemia, (8) nonspecific serologic reactions for syphilis, (9) disappearance of the facial eruption, leaving no atrophy or other residua, with fatal progression of the disease.

There was no history of unusual photosensitivity, so frequently present in cases of acute disseminated lupus erythematosus. Petechiae were observed, but, as Libman has pointed out, caution must be exercised in interpreting their significance when they are found in or close to areas of skin affected by the disease.

The final diagnosis was arrived at with some difficulty, though it was considered from the time of admission. Erythematous rashes of the type

present in this case and progressive renal damage do not typically occur in rheumatic fever, nor was there other clinical evidence to substantiate that diagnosis. Pericarditis seldom occurs as part of subacute bacterial endocarditis, and repeated cultures failed to reveal any organism in the blood of this patient. A diagnosis of typhoid or paratyphoid fever, undulant fever or tularemia could not be sustained in the presence of negative serum agglutination tests. The Frei and tuberculin tests were negative. Biopsy failed to reveal the presence of periarteritis nodosa. In the absence, then, of any other definite etiologic factors, the combination of a febrile illness with an erythematous facial eruption, together with arthralgia, pericarditis, negative blood cultures and evidence of renal damage and bone marrow depression, seemed definitely to point to disseminated lupus erythematosus of the systemic type. The fact that a biopsy revealed nontuberculous lymph node lesions of the type seen in undoubted cases of the disease definitely confirmed this diagnosis.

Grossly, no conspicuous changes, aside from the bronchopneumonia (evidently terminal) and cardiac hypertrophy and pericarditis, were noted at autopsy. However, microscopic study revealed widespread lesions involving the vascular system (particularly the renal glomeruli), heart, lymph nodes and spleen.

The glomerular lesions were essentially of the type described first by Baehr, Klemperer and Schifrin [5] and later by Klemperer in the case reported by Denzer and Blumenthal.[9] As Klemperer pointed out, these glomerular alterations are distinctly unusual. They do not resemble those found in the glomerulitis in general infections described by Bell [10] or in glomerulonephritis. It is probable that the development of the glomerular changes is analogous to that of the endocardial changes to be described; thus one of the most characteristic pathologic changes in this disease is represented by a process of endothelial and mesothelial swelling, proliferation, degeneration, necrosis and reactive inflammation.

The changes in the heart bore no resemblance to those of rheumatic heart disease, nor did they appear to be of bacterial origin. Our study of the endocardial lesions led us to believe that they were essentially of the type described by Gross [4, 6] in studies of Libman-Sacks disease with and without lupus erythematosus and of disseminated lupus erythematosus with and without atypical verrucous endocarditis. Other cases of disseminated lupus erythematosus with endocardial lesions probably related to but not identical with those described by Libman and Sacks

9. Denzer, B. S., and Blumenthal, S.: Acute Lupus Erythematosus Disseminatus, Am. J. Dis. Child. **53**:525 (Feb.) 1937.

10. Bell, E. T.: The Early Stages of Glomerulonephritis, Am. J. Path. **12**:801, 1936.

have been reported by Pernet,[8b] Belote and Ratner,[11] Jarcho,[12] Rose and Goldberg,[8p] Weidman and Gilman [13] and others.

The microscopic endocardial changes undoubtedly serve as the basis for the subsequent development of the gross verrucous lesions, though it is possible that such microscopic lesions may heal. Indeed, the possibility of healing of atypical verrucous endocarditis has been considered by Libman.[2c, 14] The appearance of these changes in the heart suggests that the initiating factor is damage to the endocardial lining by an as yet unascertained toxic agent. This primary involvement of the endothelium is clearly brought out in the studies of Gross;[6] it differs from the mode of attack in rheumatic fever, in which the endothelial changes are secondary to inflammatory involvement of the valve rings and valves. The pathogenesis of the pericarditis appears to be essentially similar. Libman has pointed out that the gross lesions in atypical verrucous endocarditis may be slight or extensive. The occurrence of microscopic lesions in the absence of gross vegetations indicates the necessity for detailed histologic study, just as does the occurrence of extensive glomerular changes in the absence of gross scarring or hemorrhage of the kidneys. In addition to the characteristic endocardial changes, a terminal nonbacterial thrombotic endocarditis may be found in this disease, as in many others.[14a]

The occurrence of the focal necrotic lesions in the lymph nodes has been mentioned,[15] but we have not found a detailed description of them. They appear to be as characteristic as the glomerular changes, though undoubtedly of less frequent occurrence. Short [16] in 1907 reported a fatal case of lupus erythematosus in a 28 year old woman in which the lymph nodes showed areas of necrosis with no micro-organisms present. The development of clinical lymphadenopathy in cases of disseminated lupus erythematosus has long been noted [15] and has frequently been

11. Belote, G. H., and Ratner, H. S. V.: The So-Called Libman-Sacks Syndrome: Its Relation to Dermatology, Arch. Dermat. & Syph. **33**:642 (April) 1936.

12. Jarcho, S.: Lupus Erythematosus Associated with Visceral Vascular Lesions, Bull. Johns Hopkins Hosp. **59**:262, 1936.

13. Weidman, F. D., and Gilman, R. L.: A Case of Acute Disseminated Lupus Erythematosus, Brit. J. Dermat. **43**:641, 1931.

14. Libman, E.: The Varieties of Endocarditis and Their Clinical Significance, Tr. A. Am. Physicians **53**:345, 1938.

14a. Friedberg, C. K.; Gross, L., and Wallach, K.: Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, Arch. Int. Med. **58**:662 (Oct.) 1936.

15. Keil, H.: Conception of Lupus Erythematosus and Its Morphologic Variants, with Particular Reference to "Systemic" Lupus Erythematosus, Arch. Dermat. & Syph. **36**:729 (Oct.) 1937.

16. Short, T. S.: Fatal Case of Acute Lupus Erythematosus, Brit. J. Dermat. **19**:271, 1907.

cited as evidence of the tuberculous nature of the disease.[17] Microscopic examination, however, may disclose the nontuberculous nature of the changes in some cases. Thus Roberts [18] reported a fatal case of acute disseminated lupus erythematosus in a 21 year old woman in which the mesenteric nodes had been considered as the seat of old caseous tuberculosis and some of the other glands as showing recent tuberculosis but microscopic study failed to reveal any evidence of tubercles or of tubercle bacilli. In our case the histologic structure of the lesions in the lymph nodes was in no way suggestive of tuberculosis, nor did specific search reveal any tubercle or other bacilli. The prevailing belief that tuberculosis is not a specific etiologic factor in the disease was thus substantiated.

Areas of focal necrosis have been noted also in the spleen (Snapper,[8o] Jarcho [12]) though not described in detail. They too appear to be a characteristic manifestation and are not tuberculous in structure. The perivascular fibrosis of the smaller arteries of the spleen has been described by Libman and Sacks [2e] in one of their cases, and by Klemperer in the case of acute disseminated lupus erythematosus reported by Denzer and Blumenthal.[9]

It is interesting that the synovial tissues of the knee joint presented few significant changes, in spite of the prominence of the arthritic symptoms, which are so frequently present in this disease. It is of course possible that in this case and in other cases other articular tissues might have shown more pronounced changes.

It is unfortunate that limitation of permission for autopsy precluded examination of the brain, since cerebral symptoms similar to those present in our case are not infrequently noted in fatal cases of the disease. They were present in such a case previously studied in this hospital. Jarcho [12] has described the occurrence in 1 of his cases of multiple small areas of encephalomalacia and of thrombi in many of the small cerebral vessels.

Finally, we note the observation of Klemperer [19] that in some cases in which the disease was acute and rapidly fatal no morphologic changes could be found in the internal organs. Such cases are indeed few and possibly are found only when the toxic process is so virulent as to produce death after an interval insufficient for the production of visible anatomic changes.

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17. Keil, H.: Relationship Between Lupus Erythematosus and Tuberculosis: A Critical Review Based on Observations at Necropsy, Arch. Dermat. & Syph. **28**:765 (Dec.) 1933.

18. Roberts, L.: Acute Lupus Erythematosus (Aigu d'Emblée), Brit. J. Dermat. **23**:167, 1911.

19. Klemperer, P., in discussion on Ginzler and Fox.[7]

REVIEW OF OTHER CASES

Lupus erythematosus was first described in the early part of the last century, by Biett, Hebra and Cazenave, as a local cutaneous disease of no prognostic concern. In a brief report in 1869 and in his classic paper of 1872, Kaposi [1] classified this dermatosis into two forms: lupus erythematosus discoides and lupus erythematosus discretus et aggregatus. He described cases, particularly of the latter type, in which the disease, unlike the ordinary chronic forms, presented evidence of grave visceral complications. The symptoms were sometimes accompanied by an erysipelas-like eruption of the face, to which he referred as erysipelas perstans faciei. The disease pursued an acute or subacute febrile course with severe toxic manifestations. In addition, Kaposi noted the occurrence of arthritis, pleuropulmonary complications and lymphadenopathy. Three of his series of 11 patients died while under observation.

After Kaposi's original contribution, similar observations were reported from time to time. The clinical picture, as described in these reports and in the dermatologic texts of the period, varied little from that recorded by Kaposi except that the frequent occurrence of renal damage was noted. In 1908 Pernet [8b] wrote his well known monograph based on 9 cases from the literature and a tenth case of his own. Pernet, however, included only cases in which the disease was acute from onset and rapidly fatal, a syndrome which he called *lupus érythémateux aigu d'emblée*. He felt that these cases formed a group separate and distinct from those in which the course was subacute, or those in which the course was acute and albuminuria was present. Such distinctions, however, do not appear to be justified, and these cases probably do not differ in nature from the cases with a subacute course or those in which there is an acute exacerbation of a chronic form of lupus erythematosus, which may have the same grave features and eventual fatal termination.

The literature for a half-century following Kaposi's report added little to knowledge of the nature and pathogenesis of the disease. During this time, particularly in the Continental literature, the disease was generally held to be of tuberculous nature, on what seems rather meager evidence. Perhaps for this reason the available pathologic material appears to have been inadequately studied, so that until recently no characteristic visceral pathologic changes had been described in detail. An exception, perhaps, is a description of the renal glomeruli by Keith and Rowntree [20] in a case of lupus erythematosus in a 20 year old woman; the renal lesions were misinterpreted, however, as those of an ordinary chronic glomerulonephritis.

20. Keith, N. M., and Rowntree, L. G.: A Study of the Renal Complications of Disseminated Lupus Erythematosus, Tr. A. Am. Physicians **37**:487, 1922.

Indeed the disease seems to have been known chiefly to dermatologists, who, it must be said, were familiar not only with the ordinary discoid type of lupus erythematosus but also with the more uncommon forms with systemic involvement, as may be seen from a perusal of the proceedings of dermatologic societies. It is not improbable, however, that patients with this disease were often seen by internists, particularly when the dermatologic manifestations were not prominent, and treated as patients with typhoid fever, rheumatic fever, scarlet fever, erysipelas, arthritis, pellagra or acute abdominal disease. Nevertheless, Keefer and Felty,[21] in 1924, described 3 cases of the disease brought to their attention for reasons other than the cutaneous manifestations; they stated the belief, after a study of their cases and those reported in the literature, that the disease was a definite clinical entity "occurring nearly always in females and characterized by fever, joint and muscle pains with swelling but without joint changes, abdominal pains, glandular enlargement sometimes associated with splenomegaly, typical disseminated skin lesions with great prostration, occasionally with delirium, secondary anemia often with normal leukocyte count, a downhill course with increasing asthenia and generally failure, and finally, exitus due to an intercurrent respiratory infection or to nephritis." They believed that the pathologic findings were neither constant nor characteristic, and that the lesions of pneumonia and nephritis, often present, could not be regarded as playing a primary role. Essentially similar conclusions were arrived at by Goeckerman,[8b] Mook, Weiss and Bromberg[22] and Madden.[8k]

As previously stated, the basis for the present understanding of the nature of this remarkable disease rests to a large extent on the observations of Libman.[2] In his studies of endocarditis he encountered a series of cases (including 1 case observed as early as 1911) in which, though showing similarities to both rheumatic and subacute bacterial endocarditis, the disease differed in certain fundamental respects from each, clinically and pathologically. In 1924 Libman and Sacks[2c] reported in detail, as instances of a clinical-pathologic entity, 4 cases of this disease in which the endocardial lesions were denoted as atypical verrucous endocarditis; this syndrome has come to be known as Libman-Sacks disease. Clinically the condition in these cases formed a well defined complex which the authors summarized as follows: "The disease in the form in which it attacked young people who had previously had no organic symptoms ran a subacute course with fever and progressive

21. Keefer, C. S., and Felty, A. R.: Acute Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. **35**:294, 1924.

22. Mook, W. H.; Weiss, R. S., and Bromberg, L. K.: Lupus Erythematosus Disseminatus, Arch. Dermat. & Syph. **24**:786 (Nov.) 1931.

anemia. Briefly enumerated, the findings were pericarditis, white-centered petechiae, arthritis, erythematous and purpuric rashes, ulcerative lesions of the mucous membranes, pleuro-pulmonary symptoms, embolic phenomena, enlargement of the liver and spleen, acute glomerulonephritis, a tendency to leukopenia, and repeatedly negative blood cultures. Two of the patients had an eruption of the face which resembled acute lupus erythematosus disseminatus." The authors emphasized the inconsistency of a diagnosis of rheumatic endocarditis when white-centered petechiae and glomerulonephritis were present, and, similarly, of a diagnosis of subacute bacterial endocarditis when erythematous rashes, pericarditis, and repeatedly negative blood cultures were present.

Pathologically, in the 4 cases verrucous endocardial vegetations were observed which differed in structure and localization from those in both rheumatic and subacute bacterial endocarditis. The lesions contained no bacteria. Aschoff bodies and Bracht-Waechter lesions were not found. There was a nonbacterial organizing pericarditis. In 2 cases there was diffuse glomerulonephritis, in 3 pleuritis, in 2 bronchopneumonia, in 1 ascites and in 3 enlargement of the spleen together with small splenic infarcts; in 1, microscopic examination revealed periarterial hyaline thickening in the spleen. The authors felt that the etiologic agent (whatever it might be) or its toxin had a great affinity for the glomerular endothelium. In 1925, on clinical grounds, Libman advanced the hypothesis that endocarditis is not an essential feature of the disease.

Gross [4] described in great detail the cardiac changes in 11 cases of atypical verrucous endocarditis. Of particular importance was the occurrence in 5 of the patients, all female, of an erythematous eruption having the appearance of acute lupus erythematosus. The 11 cases included the 4 of Libman and Sacks, in 2 of which the eruption was noted. Both Libman and Sacks and Gross recognized the possible significance of this symptom.

In 1931, in a report on renal complications in 17 cases of Libman-Sacks disease, Baehr [3] concluded that the disease is an expression of a systemic process affecting the capillaries and finer ramifications of the vascular tree, in which toxic damage produces swelling, proliferation and necrosis of the vascular endothelium. Significantly, because of 2 additional cases in which no endocardial lesions were present, Baehr stated the opinion that endocarditis is not an essential feature of the disease, and may be absent in cases in which one finds the typical changes in the skin, kidneys and other viscera.

An important advance was made in 1935 by Baehr, Klemperer and Schifrin.[5] They summarized the clinical and pathologic findings in a series of cases which presented the complete clinical picture, including

the cutaneous lesions, of disseminated lupus erythematosus. Of particular importance is their description of the peculiar vascular lesions, and especially the glomerular lesions which, when present, are so characteristic. They summarized the clinical course as "characterized by a more or less prolonged, irregular fever with a tendency to remissions of variable duration . . ., by involvement of synovial and serous membranes . . ., by depression of bone-marrow function . . . and by clinical evidences of vascular alterations in the skin, the kidneys and the other viscera. The disease often ends fatally after a period varying from four weeks to five years." Twenty-two of their 23 subjects were females; in the case of the 1 male patient the diagnosis was made on the basis of an atypical erythema of the face, and was considered to be doubtful.

Pathologically, there was evidence of pleuritis, pericarditis or both in 17 cases. A coarse nonrheumatic, nonbacterial verrucous endocarditis was present in 13 cases, in 5 of which it conformed exactly to the picture of atypical verrucous endocarditis in Libman-Sacks disease. Aschoff bodies were not found. Tuberculosis was absent in all but 2 cases; in 1 a single caseous tracheobronchial lymph node was observed and in the other there was terminal miliary tuberculosis after more than a year of debilitating illness. Remarkable vascular lesions were revealed microscopically throughout the finer ramifications of the systemic and sometimes also the pulmonary circulation. These consisted of: (1) simple dilatation of the capillary bed in certain areas, as in the skin, with bloody and serous extravasations; (2) proliferative lesions of the lining endothelium of capillaries, arterioles and venules, associated with thrombi which often obstructed or occluded the lumen, and (3) degenerative and necrotizing lesions in the wall of such vessels, associated with thrombosis and sometimes with hemorrhage into the adjacent tissues.

Glomerular changes, consisting of proliferative and thrombotic lesions of the capillary loops, were conspicuous in most cases. In particular the authors noted a peculiar hyaline thickening of the capillary walls which they called the "wire-loop" lesion. This lesion had not been seen by them in any other human disease and was approached only in eclampsia. The authors stated the belief that these patients had been suffering from a peculiar constitutional reaction to a low grade infection, and that the disease was not conditioned by the nature or severity of the local infection or intoxication but seemed rather to depend on some peculiarity in the constitutional reaction of the host. It is important to emphasize here that Libman, as well as Baehr, Klemperer and Schifrin, observed cases indicating that essentially the identical disease may occur in subjects in whom the cutaneous eruption never develops.

Comparison of the clinical and pathologic details observed in cases of disseminated lupus erythematosus, on the one hand, and of atypical verrucous endocarditis on the other, and study of the conclusions as to the essential nature of the process in the two diseases clearly indicate that they are closely related if not actually identical. Gross [6] compared the cardiac lesions in 23 cases of disseminated lupus erythematosus with those in 4 cases of Libman-Sacks disease without lupus erythematosus. In the former group, he noted macroscopic lesions in 9 cases and microscopic lesions in most cases; with few exceptions, he considered these lesions to be characteristic of the group and in many instances identical with the lesions found in the cases of atypical verrucous endocarditis. Gross concluded that the two diseases are essentially the same and should be placed in the single category of Libman-Sacks disease. We believe it is likely that the condition classified by Friedberg, Gross and Wallach [14a] as nonbacterial thrombotic endocarditis associated with prolonged fever, arthritis, inflammation of serous membranes and widespread vascular lesions also belongs in this category. Indeed, we are informed that a reexamination of the cases of this condition has disclosed the characteristic lesions in 3 of the cases; in the fourth, insufficient material remains available.[24]

Other cases that undoubtedly are also instances of this disease have been reported in recent years by Tremaine [25] and by Christian,[26] similarly under somewhat obscure titles. Nevertheless, that there is a growing appreciation of the essential similarity of the syndromes in spite of some variations in symptoms is evidenced in a recent paper by the Reifensteins [27] in which an excellent selection of cases from the literature is described.

In regard to the etiology of the disease there is little to offer save conjecture. As we have indicated, the evidence in favor of tuberculosis as a specific causative factor is unconvincing. It rests on the occasional association of the disease with tuberculids, the presence of scrofulous

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23. Footnote deleted.

24. Friedberg, C. K.: Personal communication to the authors.

25. Tremaine, M. J.: Subacute Pick's Disease (Polyserositis) with Polyarthritis and Glomerulonephritis, New England J. Med. **211**:754, 1934.

26. Christian, H. A.: Long-Continued Fever with Inflammatory Changes in Serous and Synovial Membranes and Eventual Glomerulonephritis: A Clinical Syndrome of Unknown Etiology, M. Clin. North America **18**:1023, 1935.

27. Reifenstein, E. C.; Reifenstein, E. C., Jr., and Reifenstein, G. H.: A Variable Symptom Complex of Undetermined Etiology with Fatal Termination, Including Conditions Described as Visceral Erythema Group (Osler), Disseminated Lupus Erythematosus, Atypical Verrucous Endocarditis (Libman-Sacks), Fever of Unknown Origin (Christian) and Diffuse Peripheral Vascular Disease (Baehr and Others), Arch. Int. Med. **63**:553 (March) 1939.

stigmas or clinically diagnosed tuberculosis, a family history of tuberculosis and the occasional demonstration at autopsy of tuberculosis, especially of the lymphatic type. The last, as we have shown, is especially open to doubt unless the diagnosis is verified by microscopic study, since the changes in the lymph nodes and spleen may simulate, especially grossly, those of tuberculosis. Certainly there is no doubt that in many cases, including the case we report here, careful search has failed to reveal any evidence of tuberculosis. The evidence that the disease is of streptococcic origin is even less convincing. In the case of our patient, repeated blood cultures were negative, and Baehr, Klemperer and Schifrin reported 36 negative cultures with specimens of blood taken from 20 patients with the disease during febrile periods. Similarly, Libman and Sacks reported negative blood cultures in their cases.

The role of such photosensitizing agents as the porphyrins, a possible etiologic factor, suggested by the frequent history of abnormal sensitivity to sunlight and similar sources of radiation, is also obscure. Hematoporphyrins have been found to be present by some investigators and absent by others. In a recently reported series of 18 cases of acute and subacute disseminated lupus erythematosus, of which 9 were known to have ended fatally, Ludy and Corson [28] found hematoporphyrinuria in 4 of the fatal cases and in 3 others; in 3 cases it was not looked for, and in the other 8 it was not found. The authors also pointed out, in connection with a suggestion that lead may play a role in the etiology of the disease, that lead poisoning is a condition in which hematoporphyrinuria may be present. They were able to demonstrate pronounced spectroscopic evidence of lead in the skin in 15 of their cases, and a trace in the other 3; while in a series of 20 controls, lead was not found in 17 and there was only a trace in 3.

As Denzer and Blumenthal have pointed out,[9] either clinical or pathologic evidence has demonstrated disseminated lupus erythematosus with a host of other conditions, such as tuberculosis, streptococcic infections, disease of the sinuses, carcinoma of the stomach, infections of the respiratory tract, pyonephrosis, dermatomyositis, scleroderma and periarteritis nodosa. It would seem, at least debatable, to conclude that such diverse associated conditions are necessarily related to the disease. On the other hand, in the continued absence of any recognizable specific etiologic factors it is reasonable to suppose that some peculiarity in the constitutional makeup of the patients with the disease might have brought about similar characteristic reactions to a variety of noxious agents. However, whether disseminated lupus erythematosus is, as

28. Ludy, J. B., and Corson, E. F.: Lupus Erythematosus: Increased Incidence, Hematoporphyrinuria and Spectroscopic Findings, Arch. Dermat. & Syph. **37**:403 (March) 1938.

MacLeod [29] has written, "a cutaneous symptom of a peculiar type which may be called forth by a variety of causes, toxic or septic" and, as expressed by Baehr, Klemperer and Schifrin, "conditioned . . . by a peculiarity in the constitutional reaction of the host," or whether, as might be suggested by the consistent clinical and pathologic picture, a uniform etiologic agent, such as a filtrable virus, is responsible, cannot now be answered.

We can conclude, much as have Denzer and Blumenthal, only that in this disease there is evoked a toxic agent which may produce widespread damage in the body, and which has a predilection for mesenchymal tissues, particularly those of endothelial and mesothelial structure.

SUMMARY

A case is presented of disseminated lupus erythematosus of the acute type in a male.

The disease occurs chiefly, though not exclusively, in females in the second to the fourth decade of life. Clinically, it often sets in with a distinctive type of erythematous cutaneous eruption; sometimes there is a history of unusual photosensitivity or preceding sunburn. The eruption, however, may not appear until some time after the onset of systemic symptoms, and undoubtedly cases may occur without the cutaneous manifestations. Another frequent initial clinical manifestation is polyarthralgia, which may be sufficiently severe to constitute an orthopedic problem.

The course of the disease is variable, being sometimes precipitous (*aigu d'emblée* type of Pernet) and sometimes drawn out, with remissions. Fever is usually present, often associated with pronounced prostration or asthenia and usually with clinical evidence of damage to serous membranes (arthralgias, pleuritis, pericarditis, ascites), depression of function of the bone-marrow (leukopenia, anemia, thrombopenia) and various hemorrhagic phenomena (purpura, petechiae, bleeding). There is usually evidence of renal damage, which may be severe. Evidence of endocarditis is less often clinically demonstrable. Enlargement of lymph nodes and, less often, of the spleen may be observed. Abdominal pain may be the basis for an erroneous diagnosis of an operable abdominal lesion.

Pathologically, there may be widespread distinctive vascular lesions, particularly of the renal glomeruli, which may show the characteristic "wire-loop" lesion described by Baehr, Klemperer and Schifrin. Nonbacterial pericarditis is common. There may be endocarditis of the type described by Libman and Sacks and by Gross, or there may be a

29. MacLeod, J. M. H.: Lupus Erythematosus, Arch. Dermat. & Syph. **9**:1 (Jan.) 1924.

terminal nonbacterial thrombotic endocarditis. The disease may occur without endocardial changes or without a cutaneous eruption, and probably both of these, or indeed any of the features mentioned, may be absent. Notable when present is the occurrence of peculiar lesions in the lymph nodes and spleen. Microscopically, in the former there are distinctive areas of focal necrobiosis with or without peculiar hematoxylin-staining bodies; in the latter there are periarterial areas of necrosis of the follicular lymphoid tissue, periarterial fibrosis and intimal arterial thickening.

The causation of disseminated lupus erythematosus is not known. In any case, the disease does not seem to be of specific tuberculous or streptococcic origin. Serologic reactions may be positive for syphilis in the course of the disease, but they should be considered nonspecific. The nature of the pathologic changes suggests that they are the effects of a circulating toxic agent which has an affinity for mesenchymal tissues, particularly for endothelial and mesothelial structures. What role may be played in the elaboration of such a toxin by a specific etiologic agent or by a variety of causes in a constitutionally predisposed person is a question that must be left for future study.

PRIMARY SARCOMA OF THE PERICARDIUM

REPORT OF A CASE

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The heart is but rarely the site of a primary neoplasm, and it seldom becomes involved by metastatic malignant tumors. It is therefore of unusual interest to both clinicians and pathologists when a tumor involving this structure is discovered. Lymburner,[1] in a review of 8,550 necropsies, found 4 cases of primary tumor of the heart and 52 cases of secondary metastatic lesions of the heart. In a review of the literature,[2] he found reports of 226 instances of primary cardiac tumors. In a review of the subject in 1931, Yater [3] found records of 46 instances of primary sarcoma of the heart. Additional cases have been reported by Morris,[4] Barnes and his associates,[5] Boman [6] and Willius [7] and from the Massachusetts General Hospital.[8] Only 11 of these were cases of primary sarcoma of the pericardium.

From the Mayo Clinic. Dr. Parker is associated with the Division of Medicine, Dr. Baggenstoss with the Section on Pathological Anatomy and Dr. Dry with the Section on Cardiology.

1. Lymburner, R. M.: Tumors of the Heart: Histopathological and Clinical Study of Four Primary and Fifty-Two Secondary Tumors of the Heart, Thesis, University of Minnesota, Mayo Foundation, March 1933.

2. Lymburner, R. M.: Tumours of the Heart: Histopathological and Clinical Study, Canad. M. A. J. **30**:368-373 (April) 1934.

3. Yater, W. M.: Tumors of the Heart and Pericardium: Pathology, Symptomatology and Report of Nine Cases, Arch. Int. Med. **48**:627-666 (Oct.) 1931.

4. Morris, J. J.: Primary Sarcoma of Heart, J. Lab. & Clin. Med. **18**:935-940 (June) 1933.

5. Barnes, A. R.; Beaver, D. C., and Snell, A. M.: Primary Sarcoma of the Heart: Report of a Case with Electrocardiographic and Pathological Studies, Am. Heart J. **9**:480-491 (April) 1934.

6. Boman, P. G.: Primary Sarcoma of the Pericardium: Report of a Case, Ann. Int. Med. **12**:258-266 (Aug.) 1938.

7. Willius, F. A.: Cardiac Clinics: XLIX. Clinic on Refractory Congestive Heart Failure of Relatively Short Duration; Comments; Postmortem Findings (Primary Fibrosarcoma of the Right Auricle), Proc. Staff Meet., Mayo Clin. **13**:331-335 (May 25) 1938.

8. Primary Sarcoma (Probably Fibrosarcoma) of the Right Auricle, Cabot Case 22491, New England J. Med. **215**:1082-1085 (Dec. 3) 1936.

The majority of primary tumors of the heart are benign. About 25 per cent are malignant. The most common malignant tumors are sarcomas. They may be classified as spindle cell, round cell or mixed cell sarcomas and most frequently arise from the auricles. The cardiac valves, the ventricles and the pericardium are less common sites of origin. Among other types of primary tumors of the heart are myxomas, rhabdomyomas, rhabdomyosarcomas, fibromas, lipomas, angiomas, hemangio-endotheliomas and lymphangio-endotheliomas.

The diagnosis of a primary tumor of the heart, because of the extreme rarity of such neoplasms and the lack of recognizable clinical criteria, is usually made by the pathologist. Yet, if the clinician would bear in mind the possibility of such a lesion whenever a clinical picture presents itself which is not explicable on the basis of one of the more common cardiac lesions, the diagnosis might be made during the life of the patient.

Symptoms and signs which are likely to arouse clinical suspicion of tumor of the heart are (1) progressive circulatory failure for which no obvious anatomic basis can be demonstrated, (2) signs pointing to valvular defects with murmurs, the character of which may change from day to day or may be unduly influenced by change in posture, (3) signs of mediastinal tumor associated with changes in the roentgenologic silhouette of the heart and (4) recurrent hemorrhagic pericardial effusion.

REPORT OF A CASE

History.—A man aged 35 had enjoyed excellent health until January 1938 (nine months prior to his admission to the Mayo Clinic), when, for three days, he complained of substernal pain aggravated by respiration and associated with dyspnea on slight exertion. These symptoms subsided and did not return until three months later, when, for seven days, similar thoracic pain and dyspnea were noted. In June the patient complained of a recurrence of this distress, associated on this occasion with fever. Examination by his physician disclosed advanced enlargement of the cardiac silhouette. After three weeks' rest in bed his condition improved and he was able to return to light work. His strength, however, never returned to normal, and dyspnea prevented his undertaking any strenuous activity.

A few weeks later he experienced sharp pain in the right portion of the thorax, augmented by inspiration and associated with cough and slight hemoptysis. The pleuritic pain subsided spontaneously. He continued, however, to have a nonproductive cough, which was aggravated by lying down, and he noted that when he assumed a recumbent position his face became red and his features distorted by swelling. This was relieved by sitting up. At night attacks of coughing occurred, and on numerous occasions the spasm of coughing precipitated sudden loss of consciousness associated with deep cyanosis of the face. To prevent these attacks, he found it necessary to sleep in an upright position.

Physical Examination.—On September 8 the patient appeared well developed and well nourished. His blood pressure was 122 systolic and 80 diastolic. Attention was immediately aroused by the objective signs of venous obstruction. The patient's cervical veins were distended, and when he lay down his face and neck became cyanotic. The heart was greatly enlarged. The area of cardiac dulness

extended to the anterior axillary line on the left and to the midclavicular line on the right. The cardiac tones were clear, and there were no murmurs. Except for rales at the base of the left lung and diminished breath sounds over the lower lobe of the right lung, no significant pulmonary signs were noted. There was a marked delay in the emptying of the veins on elevation of the arm. A teleroentgenogram of the thorax disclosed a huge enlargement of the cardiac silhouette (fig. 1). The heart measured 11 cm. to the right and 15 cm. to the left of the midsternal line, and the diameter of the thorax was 34 cm. In the right lung there was interlobar pleural thickening, and at the level of the fifth rib there was a region of localized infiltration. The roentgenologist, who carried out a fluoroscopic examination of the heart, noted a diminution in the amplitude of

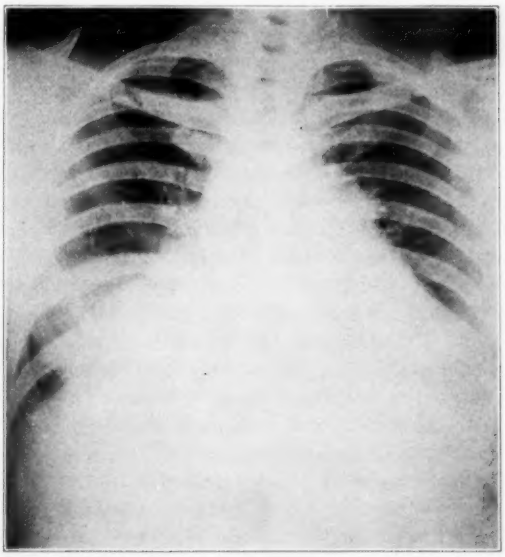

Fig. 1.—Teleroentgenogram of the thorax, showing the massive enlargement of the cardiac silhouette.

contraction in all chambers and suggested the existence of pericardial effusion. The electrocardiogram showed a sinus rhythm, slurred QRS complexes in derivations I, II and III, right axis deviation and inverted T waves in derivations II and III. The T wave was positive in the standard fourth lead. The results of routine examinations of the urine and blood, including serologic examinations, were negative.

In brief, the clinical picture was that of cardiac decompensation which had developed relatively rapidly in a comparatively young man who had experienced several episodes of retrosternal thoracic pain aggravated by respiration. On one occasion he experienced pain of pleuritic character in the right portion of the thorax associated with hemoptysis. Objectively, the striking signs were obvious and unduly marked venous engorgement, marked cardiac enlargement, with fluoroscopic evidence of diminution in the amplitude of cardiac contraction, and an electrocardiographic pattern signifying predominant strain of the right ventricle.

Course.—The patient was hospitalized for further study, and an attempt was made to alleviate congestive failure. After administration of digitalis and intravenous administration of mercurial diuretics, moderate diuresis was provoked and temporary improvement resulted. The venous pressure, however, remained high (300 mm. of water), an observation which we were led to believe indicated mechanical obstruction to the return circulation rather than an elevation caused by congestive failure alone. Paracentesis of the pericardium was performed, but it did not reveal fluid in the pericardial sac. Further efforts to control cardiac failure met with no success. He became more cyanotic, in spite of the administration of oxygen, and died seventeen days after admission to the hospital.

Speculation as to the causative background of this striking clinical picture included consideration of all possible causes of cardiac enlargement in a person whose history prior to the onset of his symptoms nine months before we saw him was singularly negative.

Valvular and congenital cardiac disease in the absence of bruits, previous hypertension in the face of a negative history, lack of retinal changes and an electrocardiographic pattern indicating strain of the right ventricle all precluded serious consideration. Nor would the cardiac hypertrophy occasionally seen after myocardial infarction fit the picture, despite a history of thoracic pain and hemoptysis (which might otherwise have been explained on the basis of pulmonary embolism secondary to dislodgment of a mural thrombus from the interventricular septum).

Still less would the pathologic entities already mentioned explain the most striking phenomenon presented, namely, the unduly high venous pressure, which was out of all proportion to the other evidences of congestive failure. This pressure had the characteristics of mechanical obstruction to the venous return rather than of venous engorgement incidental to myocardial failure; and, in view of the fluoroscopic observation of limitation in the excursions of cardiac contractions, the picture of constricting pericarditis was strongly suggested. While the possibility that this constricting factor might actually be a primary malignant process had been casually mentioned in discussion, it was not seriously considered in the clinical evaluation of this case. Perhaps one of the main reasons for failing to arrive at the correct pathologic diagnosis—indeed a reason that actually was misleading—was the electrocardiographic pattern. Thus, the evidence in favor of hypertension within the pulmonary circuit was seriously considered because of the electrocardiographic observations, in conjunction with the extreme cyanosis and the marked venous congestion. A case reported by Barnes and Yater,[9] in which multiple thrombi in the pulmonary arteries gave

9. Barnes, A. R., and Yater, W. M.: Paroxysmal Tachycardia and Alternating Incomplete Right and Left Bundle-Branch Block with Fibrosis of the Myocardium: Failure of the Right Ventricle Due to an Ancient Thrombus in the Pulmonary Arteries; Fibromyxoma of the Left Auricle Occluding the Mitral Orifice, and Simulating Mitral Stenosis, M. Clin. North America **12**:1603-1615 (May) 1929.

rise to congestive heart failure, with cardiac hypertrophy and clinical and electrocardiographic evidence of strain on the right ventricle, illustrates this syndrome.

The other known causes of pulmonary hypertension did not seem adequate to explain our findings. Appreciable emphysema was not evident, certainly not enough to produce severe pulmonary hypertension. In cases of advanced primary pulmonary arteriolar sclerosis with failure of the right ventricle, a prolonged history of progressive dyspnea prior to the onset of congestive failure is usually noted. Even assuming the possibility of thrombosis, in situ, of a branch of the pulmonary artery, which was suggested by points already mentioned, we could not expect hypertension in the lesser circulation alone to produce the extreme cardiac hypertrophy noted in this instance.

Similarly, pericarditis with massive effusion would explain the dramatic enlargement of the cardiac silhouette associated with signs of circulatory obstruction. This condition, however, was excluded by the performance of paracentesis of the pericardium. Our failure to find fluid in the pericardial sac in this instance did not exclude the possibility of pericardial disease. In cases of constrictive pericarditis associated with calcification of the pericardium, the heart is seldom found to exhibit marked hypertrophy. However, in the presence of chronic adhesive pericarditis, with or without rheumatic valvular deformities, the heart may be markedly enlarged. It has already been mentioned that examination of our patient did not disclose physical findings indicative of valvular deformity. It is, of course, not unusual to find modification of the classic auscultatory signs of valvular deformities when congestive cardiac failure is present. Occasionally, the physician may be amazed to observe at autopsy advanced valvular disease, of which, because of the disturbed cardiac dynamics associated with congestive cardiac failure, the usual signs were either absent or so minimal during the patient's life as to be considered insignificant. In estimating the condition of this particular patient, however, it seemed to us that the recent onset and rapid progression of cardiac disability in the absence of positive auscultatory signs were not in accord with a diagnosis of valvular disease.

We attempted to evaluate these possible causative factors in the light of the essential observations made during examination of this patient. It was our impression that the most logical explanation of the cardiac hypertrophy associated with venous circulatory obstruction was constrictive mediastinopericarditis.

Necropsy.—The body weighed about 180 pounds (81.6 Kg.). There was about 100 cc. of clear yellow fluid in the peritoneal cavity. When the pleural cavities were opened, a large mass was seen to fill the middle portion of the mediastinum

and a large part of the left side of the thorax. The mass appeared to be enclosed within a distended pericardial sac, which measured 21 cm. transversely. This mass compressed the left lung, especially the lower lobe, which was collapsed. The right pleural cavity contained 1,200 cc. and the left 200 cc. of clear brown fluid. The mass within the pericardial sac was firm and solid except for a portion near the base of the heart, which was fluctuant. Attempts to open the pericardial sac in the usual manner were unsuccessful, because the parietal pericardium was firmly adherent to the underlying tissue. When the fluctuant portion was opened, a large amount of thick, reddish gray gelatinoid material escaped.

The entire mediastinal mass was dissected and removed from the body. During this procedure, the left jugular and both innominate veins were seen to contain mural thrombi which extended down into the superior vena cava and almost completely blocked the lumens of these veins. The entire mass weighed 3,000 Gm. It presented an irregularly ovoid shape and measured 23.5 by 21 by 9.5 cm. (fig. 2). Superiorly, it extended 2 cm. above the bifurcation of the trachea, but nevertheless

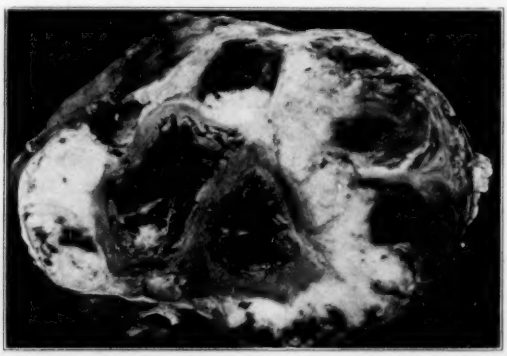

Fig. 2.—Cross section of the mass of the tumor, showing the heart encased by the neoplasm. Note the neoplastic invasion of the left ventricle.

seemed to be enclosed by a fibrous capsule, which was presumably the pericardium. Laterally, it had grown into the hilar regions of both lungs, without, however, metastasizing to the lymph nodes. Inferiorly, it was attached to the diaphragm. Posteriorly, it surrounded and compressed the pulmonary blood vessels.

On cross section it was seen that a yellowish white tumor mass completely encircled the heart and filled and distended the pericardial sac. In some regions, this tumor tissue was firm, while in other regions it was soft and encephaloid. Large and small areas of hemorrhage were situated throughout the tumor. Some of them apparently had been present for some time, as evidenced by their yellow, brown and orange discoloration. Firm white bands of fibrous connective tissue extended through the tumor.

Serial cross sections revealed the fact that the tumor reached its greatest size in the region lateral to the left ventricle, where it measured 12 cm. in thickness. Around the base of the heart and in the region of the right ventricle, the encircling sheath of tumorous tissue varied from 1 to 5 cm. in thickness. The tumor as a

whole was rather sharply demarcated from the heart muscle but in some portions appeared to invade it. The tumor appeared to be entirely enclosed within the pericardial sac, except in both hilar regions of the lungs, where it had broken through. The hilar lymph nodes were not, however, invaded by the tumor. Superiorly, the tumor surrounded the great blood vessels and compressed them somewhat.

The heart muscle was reddish brown and exhibited no gross lesions. The valves and the endocardium appeared normal.

The remaining organs disclosed nothing of note except slight evidence of chronic passive congestion in the lungs and liver.

The diagnoses from an anatomic point of view were sarcoma of the pericardium with invasion of the heart; thrombosis of the left jugular and innominate

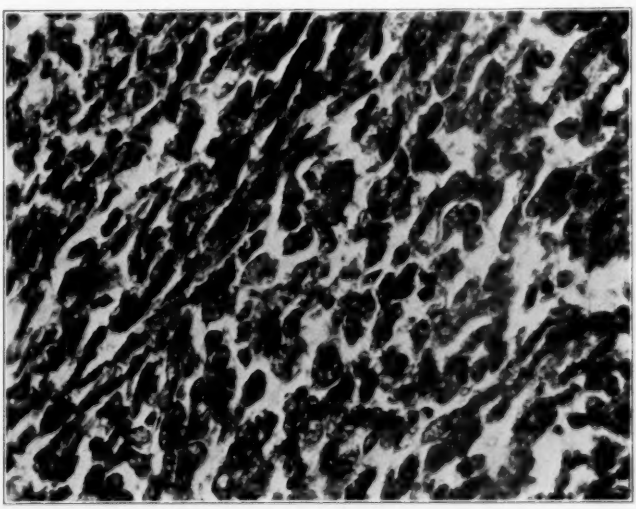

Fig. 3.—A section through the sarcomatous portion of the pericardium, showing the parallel arrangement of the spindle-shaped and oval cells (× 500).

veins and the superior vena cava; hydrothorax, with 1,200 cc. of fluid on the right and 200 cc. on the left; ascites, with 100 cc. of fluid; atelectasis of the lungs, and chronic passive congestion of the lungs and liver.

Microscopic Examination.—The structure of the tumor was uniform. It consisted of large spindle-shaped and oval cells arranged for the most part in parallel rows (fig. 3). The cells had a narrow zone of pink-staining cytoplasm, which tapered at the ends and occasionally extended out into long fibrils. In many regions the cells were closely packed, and distinct cell boundaries were difficult to delineate. The nuclei were large, spindle-shaped or ovoid, and pale staining. The chromatin was arranged in a network with occasional condensations, especially at the nuclear membrane. Nucleoli were infrequent. Mitotic figures were numerous.

Sections impregnated with silver by the Bielschowsky technic revealed many fine fibrils in close association with the tumor cells. These reticular fibrils were hypertrophied at the borders of the cardiac muscle and in the regions where they became continuous with the connective tissue septums of the tumor. The fibers of the reticulum were larger and more numerous between the fibers of the cardiac muscle than they were in the tumor.

Evidences of degenerative cellular changes, such as pyknosis and karyorrhexis, were diffusely scattered throughout the tumor, and in some portions distinct foci of necrosis were seen. Hemorrhages were numerous.

Sections which included both the tumor and the cardiac muscle disclosed invasion of the myocardium (fig. 4). In some regions, the muscle cells were completely surrounded by neoplastic cells. There was destruction of the muscle cells with proliferation of fibrous connective tissue.

Fig. 4.—A section through the myocardium, showing invasion of that muscle by sarcomatous spindle-shaped cells.

COMMENT

In the light of the necropsy, the clinical picture is easily understood.

The thoracic pain may be explained by the malignant process in the pericardium. The apparent progressive massive cardiac enlargement, together with the roentgenoscopic finding of diminished amplitude of cardiac contraction, likewise is explained by the tremendous tumor in which the heart was encased. The venous obstruction was, as we had thought, the result of mechanical obstruction of the large veins which enter the heart. There was not sufficient displacement in the anatomic axis of the heart to account for the finding of right axis

deviation in the electrocardiogram. Yet this sign, together with the negativity of the T wave in leads II and III, may be accounted for by the manner in which the mass of the tumor had surrounded and compressed the great blood vessels at the base of the heart, especially the pulmonary vessels, throwing a strain predominantly on the right ventricle.

We believe that the episodes of loss of consciousness were the result of cerebral anoxemia secondary to venous stasis. Other instances are on record [10] in which attacks of unconsciousness were associated with extreme cyanosis. Their relation to posture is explained by the increased or decreased venous drainage dependent on gravity. Thus, all the features of this case which had proved to be so perplexing from the standpoint of clinical diagnosis became explainable in the light of the pathologic observations. We feel that had we not been unduly influenced by the extreme rarity of primary cardiac neoplasms and had we discounted certain confusing features in the electrocardiographic pattern, the correct diagnosis might have been made during the life of the patient.

10. Montgomery, G. L.: A Case of Pulmonary Artery Thrombosis with Ayerza's Syndrome, J. Path. & Bact. **41**:221-230 (Sept.) 1935.

EVALUATION OF THERAPY IN MYASTHENIA GRAVIS

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The disease entity known as myasthenia gravis was first described by Willis [1] in the seventeenth century. Although this condition is relatively easy to recognize clinically, its cause has remained obscure. Pathologically in many cases there are variable degrees of nonspecific degenerative muscle atrophy. In more than 50 per cent of cases focal collections of small round cells have been observed in muscles and other organs. These small foci of cells have been termed "lymphorrhages" and when present are diagnostically significant. A relatively large number of cases have been reported in which thymic neoplasms existed. The conspicuous symptomatic features of myasthenia gravis are excessively rapid fatigability of muscles in action and quick restitution of function on relaxation. The muscular exhaustibility may be elicited in the form of a characteristic electrical reaction which has been termed the Jolly reaction.

In this article no effort will be made to discuss in detail the etiology, pathology, semiology and diagnosis of myasthenia gravis. For such a discussion the reader is referred to the excellent review of the subject published by Keschner and Strauss.[2] The present study is primarily concerned with the question of treatment of this disease. Therapy has been largely ineffective until recently; in recent years, however, there have been increasingly numerous reports describing beneficial effects following the administration of a wide variety of drugs, including aminoacetic acid, ephedrine, extract of the anterior lobe of the pituitary gland, physostigmine, prostigmine and potassium chloride. Some reports with regard to a few of these remedies have contradicted the favorable reports made by others using the same drug. In interpreting such contradictory reports one must remember that falsely beneficial results may have been obtained because of the spontaneous remissions which are apt to occur

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1. Willis, cited by Guthrie, G. L.: "Myasthenia Gravis" in the Seventeenth Century, Lancet **1**:330 (Jan. 31) 1903.

2. Keschner, M., and Strauss, I.: Myasthenia Gravis, Arch. Neurol. & Psychiat. **17**:337 (March) 1927.

in this condition. One must also consider the fact that considerable difficulty may be encountered in differentiating clinically between myasthenia gravis and the myasthenic syndrome due to encephalitis or to other specific etiologic factors.

In determining the effect of therapy, some observers have utilized the response to various functional tests for motor power and fatigue. Others have emphasized subjective alterations in the patient as a means of judging the effectiveness of treatment. It would seem that in order to evaluate properly the results of therapy it is necessary to have some objective index of the patient's muscular strength. This index should be capable of standardization as far as possible and should thus be valid for comparison in the individual patient. With this view in mind, certain test procedures have been selected for the measurement of muscle power and fatigue. This study consists of the utilization of such tests in order to evaluate the relative effectiveness of certain forms of therapy that have been proposed. A group of 7 cases in which the diagnosis of myasthenia gravis was clearly established has been used in this investigation. The results in each case have been tabulated (tables 1 to 7).

The remedies which were administered to the various patients consisted of aminoacetic acid, ephedrine, a combination of aminoacetic acid and ephedrine, anterior pituitary extract,[3] prostigmine and a combination of prostigmine and ephedrine. These drugs were given successively for periods approximating one month each. Whenever possible, an initial period of one month without medication was used as a control for each patient. For various reasons (noted in the description of each case) it was not possible to give all of the aforementioned remedies in each case. The period of medication with anterior pituitary extract approximated ten days instead of one month. In instances in which prostigmine was administered parenterally, examination was made one hour after the injection. For all other forms of therapy examination was made at 9 a. m., the patient remaining in bed until this hour.

The dosage of various medications administered during the course of this study was as follows: aminoacetic acid, 10 Gm. three times a day; ephedrine, 0.03 Gm. three times a day; anterior pituitary extract, 1 cc. by hypodermic injection twice a day; prostigmine methylsulfate (1:2,000), 3 cc. by hypodermic injection, and prostigmine bromide, 90 to 165 mg. daily by mouth (given three or four times a day).

TEST PROCEDURES

A preliminary trial period during which a wide variety of test procedures were used for patients with myasthenia gravis and for controls served to eliminate

3. The form of extract of the anterior lobe of the pituitary gland used in this study was antuitrin.

a number of tests that were found to be unsatisfactory. In the more reliable test procedures the factor of dependence on the patient's cooperation, although still present to some extent, was minimized. Standardization of other variable factors was attempted whenever possible. Patients were always examined at the same time of day. Excessive clothing was removed, and draping of the body was designed to allow complete freedom of motion of all extremities. Test procedures were performed in the same sequence at each examination. Each test was done twice at every examination, and the maximum result was always taken as the one for comparison. All dynamic tests were timed so that the speed of performance could thereby be standardized. During an examination the patient was seated in a chair the seat level of which was 47 cm. from the floor.

In choosing satisfactory test procedures, the greatest difficulty was encountered with the muscles innervated by the cranial nerves. Quantitative measurements of blinking, squinting and biting were attempted but proved to be unreliable because of the excessive variability of reaction. Protrusion of the tongue was found to be the only satisfactory method of testing the strength of the bulbar muscles. This procedure has been termed the dynamic lingual test and consists of repetitive, forcible protrusions of the tongue at a definite rate of speed continuing until weakness prevents protrusion beyond the margins of the lips.

Less difficulty was encountered in choosing reliable tests of motor power in the extremities. The static arm test consisted of continuous abduction of the extended arm while supporting a hand weight of 1,000 Gm. above a level of 84 cm. from the floor; the test was terminated on inability to maintain this level. Similarly, the static leg test consisted of continuous elevation of the extended leg above a level of 43 cm. from the floor; the test was terminated by inability to maintain this level.

The dynamic arm test consisted of repetitive elevation of the extended arm from the knee to a vertical position at a definite rate of speed; the test was terminated by failure to elevate the arm completely. The dynamic leg test consisted of alternate extension-flexion movements at the knee at a definite rate of speed; the test was terminated by inability to continue this procedure. Similarly, the dynamic forearm and toe tests, which were used in 1 case, consisted of alternate extension-flexion movements at a definite rate of speed, continued to exhaustion. In a number of cases the power of the hand grasp was determined by means of a dynamometer. The average of four alternately successive attempts was used as the basis for comparison. The dynamometer has been used also to determine the duration of effect resulting from the hypodermic administration of prostigmine.

REPORT OF CASES

CASE 1.—H. A., a man aged 51 years, a carpenter, was admitted to the Montefiore Hospital on Oct. 29, 1934. He had had typhus fever at 15 years of age and frequent colds since early childhood. At various times he had had operations, including bilateral herniorrhaphy, removal of a testicle and appendectomy. In 1914 he had sharp pains in both shoulders, which persisted until 1922 and subsequently recurred infrequently. In 1934 he had general malaise without any specific complaints. In April there was sudden onset of pain in the right side of the chest, radiating to the right shoulder and arm and associated with slight fever. One month later a dull pain in the back of the neck appeared and was accompanied by a sensation of heaviness, with difficulty in lifting the head; difficulty in mastication and dysphagia soon appeared. The speech became nasal. Weakness of the left arm developed and was soon followed by weakness of the right arm. All of

these symptoms became worse, and in addition there were dropping of the lower jaw, drooling of saliva, ptosis on the left and episodes of dyspnea.

The significant physical findings on the patient's admission to the hospital were weakness of the body musculature generally with rapid fatigability; weakness of the facial muscles with inability to close the eyes; weakness of the muscles of mastication and of the tongue, and nasal speech.

Laboratory Data.—Urinalysis and a blood count gave results within normal limits. The value for blood sugar was 100 mg., that for urea nitrogen 13.8 mg., that for calcium 11.5 mg. and that for phosphorus 4.6 mg., per hundred cubic centimeters. Serologic examination of the blood and of the spinal fluid did not reveal syphilis. A myasthenic electrical reaction was obtained in the muscles of the left upper extremity.

Course.—Previous to the period of experimental therapy the patient received combined aminoacetic acid and ephedrine medication, with resultant improvement. When all medication was withdrawn the patient complained bitterly of increasing

TABLE 1.—*Results of Therapy in Case 1* *

		Medicament			
		None	Aminoacetic Acid	Ephedrine	Aminoacetic Acid Plus Ephedrine
Tongue		60 1:05	55 1:00	63 1:05	77 1:20
Arms (static)	Right	:23	:20	1:40	1:48
	Left	:17	:20	1:20	1:42
Arms (dynamic)	Right	25 :33	23 :33	59 1:20	80 1:40
	Left	19 :25	19 :27	36 :45	67 1:27
Legs (static)	Right	:36	:35	:52	:56
	Left	:45	:42	:57	:58
Legs (dynamic)	Right	47 1:08	32 :40	58 1:14	58 1:17
	Left	40 1:08	31 :45	39 :53	58 1:16

* In tables 1 to 7, inclusive, the numbers represent the period (in minutes and seconds) during which the patient was able to maintain the muscular effort required by the test.

weakness, dysphagia and dyspnea. During the period of aminoacetic acid therapy weakness persisted and there was a loss of 9 pounds (4.1 Kg.) in weight. During the period of ephedrine therapy there was a definite increase in strength, noted chiefly in the extremities. During the period of combined aminoacetic acid and ephedrine therapy this improvement persisted and was accompanied by improved speech and subsidence of dysphagia. Subsequently the patient was given prostigmine by injection but had an unfavorable reaction. He complained of marked nausea and colicky abdominal pain starting one-half hour after the injection and lasting two hours. Further use of prostigmine was refused by the patient. He was discharged on Dec. 8, 1935.

Comment.—The objective results of therapy in this case are shown in table 1. The beneficial effect of ephedrine therapy was conclusively demonstrated. Aminoacetic acid therapy alone was apparently ineffective. The slightly greater benefit obtained with combined medication as compared with ephedrine medication may possibly be due to the more prolonged use of the latter.

CASE 2.—A. M., a man aged 63 years, was admitted to the Montefiore Hospital on Aug. 8, 1935, with a history of nuchal pain beginning in May 1934 and soon followed by weakness in closing the jaws. The pain subsided, but drooping of the left eyelid appeared. In August diplopia was noted and was gradually followed by dysphagia, nasal regurgitation and thick speech. All of these symptoms became more marked. In May 1935 there was an episode characterized by the sudden onset of abdominal pain and dyspnea; this was diagnosed as a "heart attack." Subsequently the nuchal pain recurred.

The noteworthy physical findings on admission were: an enlarged heart with generalized arteriosclerosis; chronic bronchitis with pulmonary emphysema; generalized motor weakness with rapid fatigability; myasthenic facies; bilateral paresis of the muscles of mastication and those of the tongue and palate; nasal dysarthric speech, dysphagia, and diplopia.

Laboratory Data.—Urinalysis and blood count gave results within normal limits. The value for blood sugar was 105 mg., that for urea nitrogen 17.1 mg., that for calcium 10.9 mg. and that for phosphorus 4.4 mg. per hundred cubic centimeters.

TABLE 2.—*Results of Therapy in Case 2*

		Medicament		
		None	Aminoacetic Acid	Ephedrine
Tongue		32 :29	34 :32	58 :42
Arms (static)	Right	:30	:46	1:13
	Left	:22	:33	:54
Arms (dynamic)	Right	34 :43	39 :55	61 1:22
	Left	31 :38	33 :43	42 :57
Legs (static)	Right	:21	:23	:37
	Left	:25	:30	:32
Legs (dynamic)	Right	30 :35	26 :31	38 :48
	Left	25 :29	27 :33	41 :49

Serologic tests of the blood and spinal fluid showed no evidence of syphilis. The basal metabolic rate was — 4 per cent. The electrocardiogram showed right axis deviation. A myasthenic electrical reaction was obtained in the facial and sternomastoid muscles. Biopsy of muscle tissue showed nonspecific degeneration.

Course.—During the period of no medication following admission to the hospital the patient displayed increasing weakness associated with paroxysmal dyspnea. During the period of aminoacetic acid medication the extremities were slightly stronger, but there was no improvement in the bulbar symptoms. During the period of ephedrine medication there was a definite increase in muscular strength generally and a diminution in the intensity of the bulbar symptoms. This improvement persisted during the short period of combined ephedrine and aminoacetic acid medication until Jan. 5, 1936, when there was a sudden exacerbation of symptoms associated with the development of pulmonary edema. Death due to coronary thrombosis occurred on January 9. In the terminal stage the bulbar symptoms could be temporarily and partially relieved by the administration of prostigmine hypodermically.

Comment.—The objective results of therapy in this case are shown in table 2. The ineffectiveness of aminoacetic acid and the effectiveness of ephedrine are conclusively demonstrated.

CASE 3.—I. K., a man aged 24, a furrier, was admitted to the Montefiore Hospital on Sept. 18, 1931. In December 1929 he noticed that his lower extremities were gradually becoming weaker. Soon afterward the lifting of light objects became difficult. Six months later there appeared generalized weakness and occasionally diplopia. During the next six months he began to stutter when fatigued, and chewing became difficult. As his condition progressed he noticed that he was generally more fatigued in the morning than in the evening.

The significant physical findings on admission were: generalized muscle weakness with rapid fatigability; bilateral ptosis with mechanically demonstrable myasthenia; multiple extraocular muscle pareses; nasal speech; dysphagia, and difficulty in chewing.

Laboratory Data.—Urinalysis showed no abnormality. The blood count was within normal limits. The value for blood sugar 82 mg., that for urea nitrogen 12.3 mg., that for calcium 10.1 mg. and that for phosphorus 3.3 mg. per hundred cubic centimeters. Serologic tests of the blood and of the spinal fluid did not reveal

TABLE 3.—*Results of Therapy in Case 3*

		Medicament						
		None	Amino-acetic Acid	Ephedrine	Amino-acetic Acid Plus Ephedrine	Anterior Pituitary Extract (Hypo.)	Prostigmine (8 Tablets)	Prostigmine (8 Tablets) Plus Ephedrine
Tongue		45 :40	44 :37	36 :29	40 :34	25 :19	81 1:01	82 :56
Arms (static)	Right	:50	:57	1:58	1:54	1:04	2:16	2:36
	Left	:40	:46	1:26	1:30	1:04	1:48	2:23
Arms (dynamic)	Right	38 :52	38 :52	42 1:02	58 1:15	37 :48	81 1:52	95 2:09
	Left	27 :36	41 :55	39 :53	48 1:02	32 :40	64 1:29	81 1:46
Legs (static)	Right	:32	:36	:58	:53	:41	1:04	1:28
	Left	:31	:30	:52	:47	:37	:50	1:07
Legs (dynamic)	Right	27 :32	34 :40	40 :43	45 :50	28 :30	71 1:15	92 1:28
	Left	26 :28	35 :38	41 :44	48 :56	34 :33	65 1:09	104 1:37

syphilis. The basal metabolic rate was — 19 per cent. The electrocardiogram showed sinus rhythm. A myasthenic electrical reaction was obtained in the left biceps and in the facial muscles.

Course.—Prior to the period of experimental therapy the patient had been treated at various times with gelatin, ephedrine or aminoacetic acid. A combination of the last two forms of medication was beneficial. When all medication was withdrawn there were marked increase in muscular fatigability, increase in diplopia and recurrence of dysphagia. During the period of aminoacetic acid medication the aforementioned exacerbation of symptoms persisted. During the period of ephedrine medication, after two weeks the patient noticed a general increase in muscular strength, particularly in the extremities, and a subsidence of dysphagia. During the period of combined aminoacetic acid and ephedrine medication the symptomatic improvement persisted. During the period of medication with anterior pituitary extract there was an exacerbation of symptoms similar to that noted when no medication was given. In response to the administration of prostigmine hypodermically there was noted within fifteen minutes a deep tingling sensation in the face and then throughout the body, which was shortly followed by an increase in strength of the muscles, including those innervated by the cranial nerves.

(fig. 1). The maximum increase in strength appeared at the end of one hour and was followed by a gradual subsidence. During the period of oral administration of prostigmine the patient noticed a definite increase in strength affecting the entire body musculature. A slight feeling of nausea was occasionally present after the administration of prostigmine. During the period of combined prostigmine and ephedrine medication the increased muscular strength seemed to last longer than it did after medication with prostigmine alone.

Comment.—The objective results of therapy in this case are shown in table 3. The ineffectiveness of aminoacetic acid and of anterior pituitary extract is clearly shown. The beneficial effect of ephedrine is demonstrated in the extremities. The striking effectiveness of prostigmine was noted both in the tongue and in the extremities. Combined

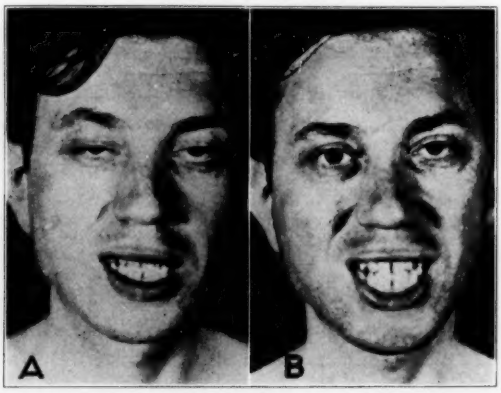

Fig. 1 (case 3).—Facial appearance of the patient (*A*) without medication and (*B*) after hypodermic administration of prostigmine.

prostigmine and ephedrine medication appeared to be slightly more potent than prostigmine therapy alone.

CASE 4.—J. W., a woman aged 45, a housewife, was admitted to the Montefiore Hospital Nov. 13, 1934, with a history of diplopia and fatigability in speaking, both starting one year previously. These symptoms were associated with gradually increasing weakness and dysphagia. There was a gradual loss of weight, amounting to 100 pounds (45.4 Kg.) previous to admission.

The significant physical findings on admission were: emaciation; generalized muscular wasting but no focal atrophies or fibrillations; generalized muscular weakness with rapid fatigability; generalized hyperreflexia; myasthenic facies; myasthenic weakness of all the musculature innervated by the cranial nerves including the eyes, face, tongue, jaws and palate; dysphagia, and nasal speech with the early appearance of aphonia.

Laboratory Data.—Urinalysis revealed no abnormality. The blood count showed: hemoglobin, 74 per cent; red blood cells, 3,030,000 per cubic millimeter;

white blood cells, 4,700 with polymorphonuclears 79 per cent, lymphocytes 13 per cent and monocytes 8 per cent. Achlorhydria was present after administration of histamine. The value for blood sugar was 88 mg., that for urea nitrogen 9.3 mg., that for calcium 9.7 mg. and that for phosphorus 5.1 mg. per hundred cubic centimeters. Serologic tests of the blood and spinal fluid serology showed no evidence of syphilis. The basal metabolic rate was 0. The electrocardiogram showed sinus rhythm. A myasthenic electrical reaction was obtained in many of the involved muscles.

Course.—Prior to the experimental period of therapy the patient received combined ephedrine and aminoacetic acid medication with resultant improvement in her condition. When all medication was withdrawn there was a marked increase in weakness together with increased dysphagia and dysarthria. During the period of aminoacetic acid medication the patient complained bitterly of increasing weakness, and she was confined to bed much of the time. During the period of ephedrine

TABLE 4.—*Results of Therapy in Case 4*

		Medicament					
		None	Aminoacetic Acid	Ephedrine	Aminoacetic Acid* Plus Ephedrine	Anterior Pituitary Extract* (Hypo.)	Prostigmine (Hypo.)
Tongue		50 :42	53 :48	42 :35	48 :45	32 :33	144 2:07
Arms (static)	Right..	1 :04	1 :07	1:08	1:11	:40	1:44
	Left....	:45	:51	1:06	1:16	:33	1:30
Arms (dynamic)	Right..	28 :42	33 :48	39 :49	41 :57	21 :31	45 :58
	Left....	23 :34	29 :42	35 :48	36 :51	18 :25	32 :38
Legs (static)	Right..	:23	:24	:26	:24	:23	:26
	Left....	:30	:36	:36	:38	:31	:40
Legs (dynamic)	Right..	32 :36	32 :33	39 :44	41 :42	20 :22	37 :37
	Left....	27 :31	30 :32	40 :43	37 :38	27 :30	43 :43
Dynamometer (hands)	Right..	35.8	37.5	44.5	44.2	27	47
	Left....	30	33.2	36.8	37	26.8	38.8

* Periods of therapy separated by an interval of three months.

medication there was a definite increase in strength generally, but the patient had many somatic complaints. During the period of combined aminoacetic acid and ephedrine medication improvement in muscular strength persisted, but the psychoneurotic manifestations continued. The patient showed a distaste for aminoacetic acid and would refuse this form of medication. During the period of medication with anterior pituitary extract there was a marked exacerbation of weakness associated with paroxysmal choking. The administration of prostigmine hypodermically resulted in marked increase in muscular strength but was accompanied by objectionable features, such as muscle contractions, diarrhea and burning on urination. As a result the patient rejected this form of medication and preferred to continue with ephedrine until her discharge from the hospital on May 28, 1936.

Comment.—This patient had pernicious anemia in addition to myasthenia gravis. She was also obviously psychoneurotic. The objective results of therapy are shown in table 4. The tests were not entirely satisfactory in this case, owing to lack of cooperation. Nevertheless,

ephedrine was shown to be effective by means of the dynamometer. The ineffectiveness of anterior pituitary extract and the comparatively striking beneficial effect of prostigmine are clearly demonstrated.

CASE 5.—S. S., a white girl aged 13 years, was admitted to the Montefiore Hospital on Feb. 22, 1935, with a history of gradual onset of hoarseness and difficulty in swallowing in the autumn of 1933. Soon afterward excessive fatigability appeared and was accompanied by diplopia, drooping of the eyelids and nasal speech. All of these symptoms improved slightly after a course of nonspecific protein therapy and then became worse. Weakness was always more marked in the evening than in the morning.

Physical examination on admission revealed the girl to be markedly undernourished. She was of asthenic habitus. There were generalized muscular weakness with rapid fatigability, particularly in the upper extremities; typical myasthenic

TABLE 5.—*Results of Therapy in Case 5*

		Medicament						
		None	Aminoacetic Acid	Ephedrine	Aminoacetic Acid* Plus Ephedrine	Anterior Pituitary Extract* (Hypo.)	Prostigmine (Hypo.)	Prostigmine (Hypo.) Plus Ephedrine
Tongue		40 :30	47 :32	50 :42	52 :45	38 :26	81 :58	100 1:22
Arms (static)	Right	:33	:22	:43	:53	:02	:58	1:12
	Left	:30	:22	:39	:43	:01	:53	:50
Arms (dynamic)	Right	38 :47	40 1:00	52 1:10	50 1:10	17 :23	66 1:31	70 1:43
	Left	35 :45	36 :48	50 1:04	47 1:06	14 :21	57 1:17	57 1:17
Legs (static)	Right	:47	1:15	1:08	1:10	:10	1:24	2:20
	Left	:50	1:18	1:12	1:02	:08	1:12	1:45
Legs (dynamic)	Right	30 :33	38 :43	38 :42	50 :52	17 :20	54 1:05	70 1:20
	Left	33 :35	45 :50	40 :47	46 :45	15 :17	54 1:00	53 :58
Dynamometer (hands)	Right	16	18.5	19.2	19.5	14.7	25.5	27.5
	Left	14.7	17.5	18.5	18.5	9.5	24.2	25.7

* Periods of therapy separated by an interval of five months.

facies; bilateral ptosis, particularly on the right; multiple extraocular muscular pareses, and weakness of the muscles of mastication and those of the palate and tongue. Early fatigability with rapid recovery on resting was demonstrable in all the paretic muscles.

Laboratory Data.—Urinalysis gave negative results. The blood count was within normal limits. The value for blood sugar was 93 mg., that for urea nitrogen 9.3 mg., that for calcium 10.9 mg. and that for phosphorus 5.2 mg., per hundred cubic centimeters. Serologic tests of the blood and of the spinal fluid revealed no evidence of syphilis. The basal metabolic rate was —11 per cent. The electrocardiogram showed sinus rhythm with low voltage.

Course.—During the initial period without medication the condition of the patient remained unchanged. During the period of aminoacetic acid medication there was no change in her condition. In spite of a special diet there was no increase in weight, largely because of the rather marked dysphagia. During the period of ephedrine medication there was a definite increase in muscular strength, which was greater objectively than subjectively. During the period of combined

ephedrine and aminoacetic acid medication improvement continued, and the patient was discharged on July 28, 1935. After her readmission on December 17 there was an exacerbation of muscular weakness accompanied by dyspnea and dysphagia during the period of medication with anterior pituitary extract. After the administration of prostigmine hypodermically there was a considerable increase in strength generally, but this could be maintained only by frequent administration of this medicament. The patient gradually became weaker but was fairly comfortable except for considerable difficulty in swallowing mucus. On March 19, 1936, there was a sudden onset of marked dyspnea. Examination revealed a massive collapse of the left lung, and death occurred on March 20, 1936. In the terminal stage prostigmine for a time was remarkably effective in relieving the patient temporarily, but finally it became ineffective.

Comment.—The age of onset of disease (11 years) in this patient is unusual. Only a few cases of myasthenia gravis have been reported as occurring in children. The occurrence of massive pulmonary collapse deserves mention as an unusual complication which should be guarded against in the case of a patient with marked dysphagia. The objective results of therapy in this case are shown in table 5. The partial benefit resulting from ephedrine therapy is best shown in tests of the upper extremities. Although the patient was in a state of relapse, the complete ineffectiveness of anterior pituitary extract and, in contrast to this, the remarkable effectiveness of prostigmine are strikingly demonstrated. Combined prostigmine and ephedrine medication apparently produces a slightly better result than does the former medication alone.

Case 6.—W. K., a man aged 29 years, a dress cutter, was admitted to the Montefiore Hospital on April 17, 1936. About thirteen years previously he had begun to notice diplopia and drooping of the right upper eyelid. At about the same time he noted excessive fatigue after an ordinary day's activity. He also had difficulty in swimming and was unable to play baseball as previously. His condition remained unchanged for four years, and then weakness became more marked. Dysphagia with nasal regurgitation of fluids appeared at that time. He was admitted to another hospital in 1926, where he was given ephedrine medication, and this was continued. However, all symptoms have persisted so that the patient has been unable to work for the past seven years.

The significant physical findings on admission were: marked weakness of all the body musculature with rapid fatigability, more marked in the extremities and more marked proximally than distally; atrophy of the paretic musculature of the shoulder girdle; myasthenic facies and weakness of the jaw muscles; weakness and atrophy of the tongue, and multiple extraocular muscle pareses, particularly in the right eye.

Laboratory Data.—A urinalysis and a blood count gave results within normal limits. The value for blood sugar was 96 mg., that for urea nitrogen 17.6 mg., that for calcium 9.4 mg. and that for phosphorus 4.3 mg. per hundred cubic centimeters. Serologic tests of the blood and of the spinal fluid revealed no evidence of syphilis. The basal metabolic rate was —12 per cent. The electrocardiogram showed marked

sinus arrhythmia. A myasthenic electrical reaction was obtained in the muscles of the right side of the face and in those of the right forearm.

Course.—During the initial period without medication there was an exacerbation of symptoms. The patient was unable to wash himself; he could walk only a very short distance; he could not raise a spoon to his mouth; he showed rapid fatigability in his speech and marked dysphagia; he could not smile, shut his eyes or whistle, and he had diplopia and complained of difficulty in evacuation of the bowel. During the period of ephedrine medication there was a gradual and considerable improvement in his strength, particularly in the extremities. This was manifested in a diminution in the intensity of many of the aforementioned manifestations. After the administration of prostigmine hypodermically there was profuse perspiration after ten or fifteen minutes and then an increase in motor power, first in the face. A maximum effect was observed at the end of one and one-half hours (fig. 2). At this time the patient would be able to smile and

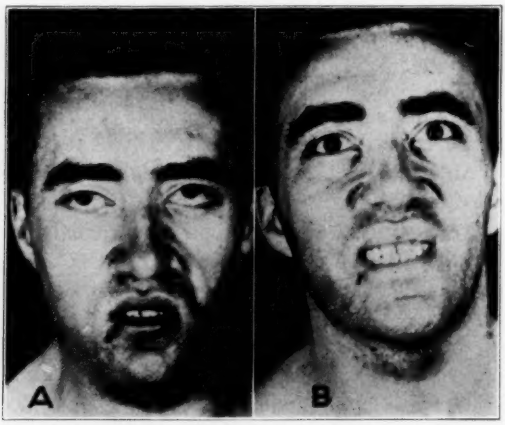

Fig. 2 (case 6).—Facial appearance of the patient (*A*) without medication and (*B*) after hypodermic administration of prostigmine.

TABLE 6.—*Results of Therapy in Case 6*

		Medicament				
		None	Ephedrine	Ephedrine Plus Prostigmine (Hypo.)	Prostigmine (8 Tablets)	Prostigmine (8 Tablets) Plus Ephedrine
Tongue		60 :24	60 :25	120 1:00	77 :37	105 :50
Arms (static)	Right	.....	:10	1:07	:12	:19
	Left	.....	.....	:58	:15	:28
Arms (dynamic)	Right	.....	5 :05	37 :55	7 :11	19 :32
	Left	.....	1 :02	35 :50	4 :07	17 :28
Legs (static)	Right	:18	:32	1:40	:35	:48
	Left	:20	:36	1:18	:37	:52
Legs (dynamic)	Right	39 :32	44 :35	160 2:20	40 :33	83 1:16
	Left	45 :35	47 :38	200 2:25	49 :38	87 1:26
Dynamometer (hands)	Right	24.2	45	78.8	41.2	77.2
	Left	25	44.5	70.2	45.5	76.2

close his eyes tightly and whistle. He would notice slight borborygmus and would be apt to have a bowel movement at this time. During the period of oral administration of prostigmine the muscular strength of the patient continued to manifest improvement, which, however, was dependent on continued administration of this drug, so that during the night there was often marked weakness. During the period of combined ephedrine and prostigmine medication the only subjective alteration consisted of a possibly more prolonged beneficial effect following each dose.

Comment.—The objective results of therapy in this case are shown in table 6. Ephedrine apparently shows its greatest effect in the extremities. Prostigmine was remarkably beneficial throughout, and striking results were obtained when it was administered hypodermically. Combined prostigmine and ephedrine therapy by mouth seems to be considerably more effective than administration of either of these medicaments alone.

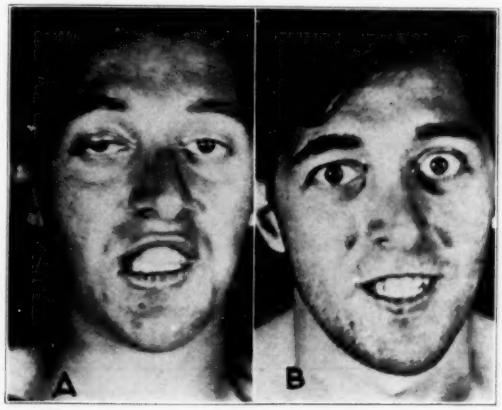

Fig. 3 (case 7).—Facial appearance of the patient (*A*) without medication and (*B*) after hypodermic administration of prostigmine.

CASE 7.—H. L., a man aged 20 years, a law student, was admitted to the Montefiore Hospital on Sept. 9, 1935. He had had poliomyelitis at 1 year of age, with residual weakness of the right leg. Subsequently he was in good health until the sudden onset of his present illness in May 1935, when he noticed blurring of vision while taking a law examination. This symptom recurred and rapidly became more marked. It was soon followed by the appearance of drooping of the eyelids and occasional diplopia. One month later weakness of both legs appeared, followed by weakness of the right arm and then of the left arm. At the same time difficulty in chewing was noted. Weakness rapidly became more marked, the patient becoming bedridden shortly before his admission to the hospital.

The significant physical findings on admission were: a sallow complexion, with some greasiness of the skin; bilateral foot drop; marked generalized motor weakness, more in the right upper extremity than in the left and increasing caudally to almost a total paralysis of both lower extremities; rapid fatigability of the paretic muscles; muscular atrophy in the right lower extremity but nowhere else; absence of the deep reflexes in the lower extremities; bilateral external ophthalmoplegia; bilateral ptosis; a myasthenic facies, and weakness of the jaw muscles.

Laboratory Data.—Urinalysis gave negative results. The blood count was within normal limits. The value for blood sugar was 86 mg., that for urea nitrogen 12.5 mg., that for calcium 12.2 mg. and that for phosphorus 5.2 mg per hundred cubic centimeters. Serologic tests of the blood and of the spinal fluid revealed no evidence of syphilis. The basal metabolic rate was —14 per cent. The electrocardiogram showed right axis deviation.

Course.—During the initial period without medication there were increasing weakness and an episode of excessive drowsiness, with constant yawning lasting

TABLE 7.—*Results of Therapy in Case 7*

		Medicament				
		None	Aminoacetic Acid Plus Ephedrine	Aminoacetic Acid Plus Ephedrine Plus Prostigmine (Hypo.)	Prostigmine (11 Tablets)	Prostigmine (11 Tablets) Plus Ephedrine
Arms (dynamic)	Right	.....	.....	10 :15	.....	.2 :04
	Left	.....	.....	18 :33	.....	4 :07
Forearms (dynamic)	Right	10 :17	16 :31	100 2:22	18 :23	21 :38
	Left	32 :40	41 1:10	100 2:08	40 1:07	100 2:13
Toes (dynamic)	Right	30 :26	50 :37	62 :52	48 :35	52 :35
	Left	47 :35	63 :45	110 1:38	60 :40	76 :45
Dynamometer (hands)	Right	.....	.....	8	.....	4.2
	Left	.....	1.2	15	.....	8.2

several days. Paroxysmal attacks of dyspnea appeared. Because of the seriousness of the symptoms, combined ephedrine and aminoacetic acid medication was instituted. He gradually showed improvement manifested by less marked fatigability and a quicker return of strength after activity. However, there was hardly any noticeable effect on the muscular strength of the lower extremities. Paroxysmal dyspnea still occurred, but less frequently. Within ten minutes after the administration of prostigmine hypodermically the patient would experience a generalized tingling in the muscles, and shortly afterward he would be able to raise his eyelids. The maximum effect would be obtained after forty-five minutes, and the duration of the effect approximated four hours. There was an improvement in muscular strength generally, but particularly in the distribution of the cranial nerves (fig. 3). Slight motion of the eyes as well as slight motion of the legs was possible during the optimum phase of improvement. During the period of oral administration of prostigmine improvement in muscular strength was also achieved, although it was less noticeable than after hypodermic administration of this drug. Evacuation of the bowel could be accomplished easily, in contrast with the difficulty noticed immediately after admission. During the period of combined prostigmine and ephedrine medication the patient subjectively seemed to experience a more prolonged beneficial effect following each dose of the former drug.

Comment.—The rapidity of progression and the intensity of involvement are unusual features. The existence of bilateral external ophthalmoplegia is also noteworthy. The objective results of therapy are shown in table 7. Myasthenia was not demonstrable by means of the dynamic lingual test; this test was therefore omitted. Combined aminoacetic acid and ephedrine therapy was mildly beneficial, and it is likely that this result was essentially due to the ephedrine. Prostigmine given by mouth produced an approximately equivalent result in the extremities but was more effective than ephedrine in relieving bulbar manifestations (not measured objectively). Prostigmine administered hypodermically was strikingly effective, in view of the almost complete incapacitation. This is well shown in table 8. The oral administration of both prostigmine and ephedrine seemed to be more beneficial than administration of the former medicament alone.

TABLE 8.—*Effect of Prostigmine (3 Ampules Hypodermically) in Case 7*

	Right				Left			
Hour	9	10	11	1	9	10	11	1
Dynamometer	0	36	25	3	0	45	36	5
	0	40	28	0	0	50	37	0
	0	35	22	0	0	54	25	0
	0	30	15	0	0	42	20	0
	0	33.2	22.5	0.7	0	47.7	29.5	1.2

GENERAL COMMENT

The treatment of myasthenia gravis has always more or less reflected the varying theories as to the pathogenesis of this disease. It is therefore pertinent to mention briefly some of these theories. For many years the condition was considered to be primarily a neurologic disorder, but no characteristic lesions were ever discovered in either the central or the peripheral nervous system. Later the discovery of lymphorrhages caused emphasis to be placed on the muscles as the primary site of disease. Subsequently the observation of an enlarged thymus gland in about 50 per cent of cases directed attention to the endocrine system.

Throughout this period, which lasted until 1930, a wide variety of remedies were used, and conflicting results were often reported. As in all debilitating diseases, tonics were extensively employed; strychnine in massive doses was particularly recommended. Diet therapy was tried by some observers, and the administration of calcium was suggested by others. Endocrine therapy of all types was resorted to, the disease being considered due to endocrine dysfunction. Beneficial effects and

complete ineffectiveness were reported by various observers as following the use of adrenal, thymic, thyroid, ovarian, testicular and hypophysial preparations.

Recently Simon [4] has described 2 cases in which subsidence of symptoms occurred after the administration of anterior pituitary extract. The present study showed a complete lack of favorable response in every case in which this aqueous solution of the adenohypophysis was used (tables 3 to 5).

Of all the forms of therapy discussed thus far, none have stood the tests of time and repeated trials. Irradiation of the thymus in cases in which this gland is enlarged has been reported as successful in a few instances but is usually ineffective. It should be emphasized that symptomatic treatment, consisting of such measures as rest, nourishing diet and good nursing care, has always been used and still is to be used in conjunction with the more specific forms of therapy.

In recent years it has been gradually recognized that a disturbance of muscle metabolism exists in myasthenia gravis. The discovery of creatine in the urine of some patients was considered as evidence in favor of such a hypothesis. In 1932, Remen [5] and Boothby [6] reported amelioration of symptoms following the administration of aminoacetic acid. Shortly before this time, Edgeworth [7] demonstrated the beneficial effect of ephedrine. Subsequently, Boothby [8] recommended the use of combined aminoacetic acid and ephedrine medication as more effective than the use of either remedy alone.

The present investigation indicates that aminoacetic acid alone is of little or no value (tables 1 to 5). The value of the test procedures utilized in this study is well illustrated in 1 case (case 1). The patient stated definitely that he felt stronger while receiving aminoacetic acid, but this subjective improvement was not demonstrated in the results of the objective test (table 1). It was just such gross unreliability that this study avoided by its manner of investigation.

Ephedrine medication alone was shown to be capable of producing considerable improvement in some cases (tables 1, 2, 3 and 6). In 2 cases the objective evidence of improvement could not be considered

4. Simon, H. E.: Myasthenia Gravis, J. A. M. A. **104**:2065 (June 8) 1935.

5. Remen, L.: Zur Pathogenese und Therapie der Myasthenia gravis pseudoparalytica, Deutsche Ztschr. f. Nervenh. **128**:66, 1932.

6. Boothby, W. M.: Myasthenia Gravis: A Preliminary Report on the Effect of Treatment with Glycine, Proc. Staff Meet., Mayo Clin. **7**:557 (Sept. 28) 1932.

7. Edgeworth, H.: A Report of Progress on the Use of Ephedrine in a Case of Myasthenia Gravis, J. A. M. A. **94**:1136 (April 12) 1930.

8. Boothby, W. M.: Myasthenia Gravis: The Effect of Treatment with Glycine and Ephedrine, Arch. Int. Med. **53**:39 (Jan.) 1934.

significant (tables 4 and 5). It would appear from this study that the good results obtained with combined aminoacetic acid and ephedrine medication are probably largely if not entirely attributable to the latter remedy alone. This is most strikingly shown in 2 instances (tables 1 and 3). The dynamic arm test in these 2 cases seemed to indicate relatively greater benefit resulting from combined medication, but confirmation was lacking in the other test procedures.

It is interesting to note that ephedrine apparently is more effective in improving the motor power of the appendicular skeletal muscles than that of the musculature innervated by the cranial nerves. In 3 patients the dynamic lingual test showed no significant evidence of benefit, which contrasted with the results of other tests (tables 1, 3 and 6). In only 1 case (table 2) did the dynamic lingual test show significant change with ephedrine therapy. No satisfactory explanation is available for the relatively greater beneficial effect of ephedrine on the muscles innervated by the spinal nerves.

Although the use of ephedrine constituted a great advance in the treatment of myasthenia gravis, within five years it was followed by an even greater therapeutic contribution. This is directly attributable to the striking advances made in knowledge regarding the chemical agents concerned in the transmission of nervous impulses. Fundamental work in this field done separately by Dale [9] and Loewi,[10] as well as more recent research, indicate that acetylcholine is liberated on stimulation of the motor nerves supplying striated muscles. It has also been discovered that physostigmine enhances and prolongs muscle contraction, apparently by inhibiting the destructive action of choline esterase on acetylcholine. These phenomena have focused attention on the myoneural junction as the probable site of the pathologic process in myasthenia gravis.

In 1934, Walker [11] reported definite improvement following the use of physostigmine in a case of myasthenia gravis. Subsequently [12] a synthetic analogue known as prostigmine (dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulfate) replaced physostigmine as the remedy of choice owing to its less toxic side effects. Numerous reports in the literature have demonstrated the remarkable

9. Dale, H.: Chemical Transmission of the Effects of Nerve Impulses, Brit. M. J. **1**:835 (May 12) 1934.

10. Loewi, O.: Ferrier Lecture on Problems Connected with the Principle of Humoral Transmission of Nervous Impulses, Proc. Roy. Soc., London, s.B **118**: 299 (Sept. 2) 1935.

11. Walker, M. B.: Treatment of Myasthenia Gravis with Physostigmine, Lancet **1**:1200 (June 2) 1934.

12. Pritchard, E. A. B.: The Use of "Prostigmin" in the Treatment of Myasthenia Gravis, Lancet **1**:432 (Feb. 23) 1935.

effectiveness of this remedy. This improvement is so uniformly observed that the injection of prostigmine in case of doubt has been proposed by Viets and Schwab [13] as a diagnostic procedure. However, it should be remembered that prostigmine causes no permanent cure; as with insulin in diabetes, continued administration is required. Progression of the disease process may result in death despite the use of prostigmine, as occurred in case 5 and as has been reported by Laurent and Walker.[14]

The present study confirms in all essential respects the many favorable reports concerning the effectiveness of prostigmine. Both the parenteral and the oral mode of administration produce excellent results; and the latter method is naturally preferable. The effect of a single dose persists for only a few hours (table 8), and therefore the drug must be given at relatively frequent intervals, usually three times a day. The degree of benefit resulting from the use of prostigmine varies greatly in different patients, and the most striking improvement is demonstrable when the drug is administered hypodermically. In contrast with the relative lack of effectiveness observed in the tongue when ephedrine is used (see foregoing sections) the noticeable benefit resulting from prostigmine is easily and often most clearly demonstrated by means of the dynamic lingual test (tables 3 to 6).

The results obtained in this study seem to indicate that combined prostigmine and ephedrine medication is more effective than use of the former remedy alone (tables 5 to 7). The combination increases both the intensity and the duration of the beneficial effect obtained from each dose of prostigmine. The combined administration of prostigmine and ephedrine is therefore recommended as the most satisfactory treatment available. The use of both these remedies has also been suggested by Boothby,[15] Laurent and Walker [14] and Macfarlane.[16]

The use of large doses of potassium chloride has been proposed by Laurent and Walther [17] as an adjuvant to prostigmine in the treatment of myasthenia gravis. Such therapy was tried in case 7 and was beneficial in that the effect of prostigmine seemed to be prolonged. How-

13. Viets, H. R., and Schwab, R. S.: Prostigmin in the Diagnosis of Myasthenia Gravis, New England J. Med. **213**:1280 (Dec. 26) 1935. Schwab, R. S., and Viets, H. R.: Prostigmin Test in Myasthenia Gravis, ibid. **219**:226 (Aug. 18) 1938.

14. Laurent, L. P. E., and Walker, M. B.: Prostigmin and Its Analogues in Myasthenia Gravis, Lancet **1**:1457 (June 27) 1936.

15. Boothby, W. M.: Myasthenia Gravis, Tr. A. Am. Physicians **51**:188, 1936.

16. Macfarlane, J. W.: Myasthenia Gravis: Its Treatment by Combination of Prostigmin and Glycine-Ephedrine Therapy, Glasgow M. J. **128**:7 (July) 1937.

17. Laurent, L. P. E., and Walther, W. W.: Influence of Large Doses of Potassium Chloride on Myasthenia Gravis, Lancet **1**:1434 (June 22) 1935.

ever, during this period there occurred unpredictable episodes of toxic manifestations.

It is interesting to note that the tests utilized in this investigation often apparently revealed the varying degree of myasthenic disease in different parts of the body musculature in each patient. This was shown by a selective lack of response to medication. For example, in 1 instance (table 4) the motor power in the legs showed no response to medication other than that which might represent a generalized weakness. In another instance (table 7) the preponderance of involvement on the right side was clearly indicated. However, one must be careful in interpretation of such varying degrees of response to medication, since a lack of response in a particular part may be due either to a localized relative sparing of musculature or to a localized relative preponderance of permanent weakness as compared with the more characteristic transient weakness which may exist in other groups of muscles. The latter element in myasthenia gravis, namely, transient weakness, may be the one which is responsive to specific medication and may therefore determine the relative value of therapy for each patient.

SUMMARY AND CONCLUSIONS

A number of reliable test procedures devised for the measurement of muscular strength and fatigability are described. In a group of 7 patients with myasthenia gravis these tests have been utilized for an objective evaluation of therapy in this disease. The various medicaments administered were: anterior pituitary extract, aminoacetic acid, ephedrine, combined aminoacetic acid and ephedrine, prostigmine and combined prostigmine and ephedrine.

This investigation leads to the following conclusions regarding therapy in myasthenia gravis: 1. Antuitrin and aminoacetic acid are ineffective remedies. 2. Ephedrine is definitely beneficial and is probably responsible for the good results obtained with combined aminoacetic acid and ephedrine medication. 3. Prostigmine is a remarkably effective remedy, and its value is enhanced when administered together with ephedrine. 4. The most satisfactory form of therapy in the absence of toxic manifestations consists of the oral administration of combined prostigmine and ephedrine medication.

ATROPHIC GASTRITIS: GASTROSCOPIC STUDIES ON THE EFFECTS OF LIVER AND IRON THERAPY

PRELIMINARY REPORT

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Chronic atrophic gastritis constitutes 13.6 per cent of gastric diseases. It is found constantly in cases of pernicious anemia, sprue and combined cord degeneration and in many cases of gastric carcinoma, in which it apparently precedes the development of the tumor. However, atrophic gastritis occurs without associated diseases and appears to be a primary disease entity. The cause is unknown; in rare cases the disease follows acute corrosive gastritis (such as that from acids or lyes), but most often chronic superficial gastritis precedes its development.

The gross anatomic features of this condition are best observed through the gastroscope. The gastric mucosa is not the orange-red of the normal mucosa but grayish pink, gray or greenish gray. It may be so thinned that the blood vessels of the submucosa become visible as blue or red arborizations. The atrophic changes are present either as sharply limited patches or as diffuse atrophic areas, which may involve the entire gastric mucosa. These changes usually are more extensive and more severe in the upper portions of the stomach. My associates and I believe that this atrophy represents an inflammatory rather than a merely degenerative process. The evidence in support of this concept will be published elsewhere.

Microscopically the outstanding feature is the thinness of the gastric mucosa, the diameter of which may be reduced to one fourth of its normal size. This thinning is due to the disappearance of the gastric glands. In the cases of most severe involvement the glands disappear completely. Remnants of crypts lie in a dense, chiefly lymphocytic, interstitial infiltration. The epithelium of these remnants of glands, as

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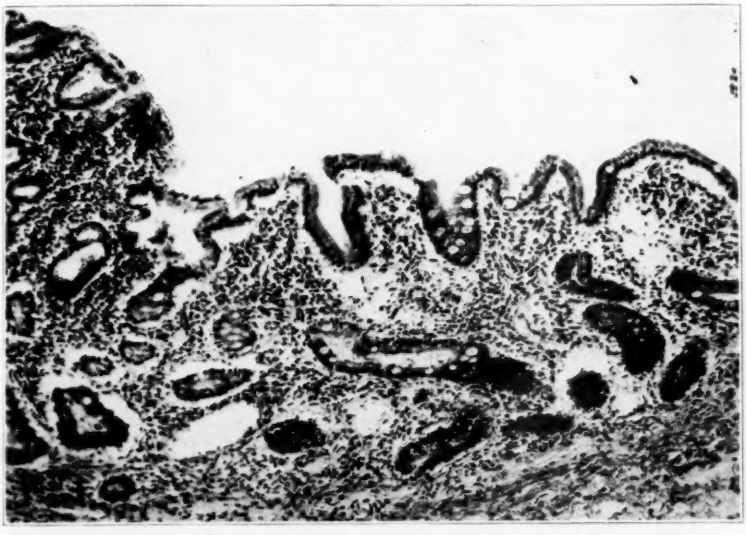
well as the surface epithelium, presents characteristic changes. In many places the normal gastric epithelium is transformed into an intestinal type of epithelium containing many goblet cells. Inflammatory changes of the submucosa and muscularis are observed even in cases of the most complete atrophy. Edema and cellular infiltration of these layers are frequent. If the atrophy is incomplete, the thickness of the gastric mucosa is not uniform. In some sections many normal gastric glands are still found, while no glands are seen in other areas, as shown in the accompanying illustration. It would seem that such atrophic changes represent the end stage of a severe inflammation and that mucosal regen-



Microscopic section of the gastric mucosa in a case of severe atrophic gastritis. The thickness of the mucosa is not uniform. The diameter at the right side is about one third and on the left side about one half its normal thickness. The normal glands are almost completely missing. The surface epithelium and the remnants of the glands contain goblet cells. There is a large amount of interstitial infiltration.

eration could not occur. However, hyperplastic proliferative nodes and pseudopolyps have been observed in some cases, evidently representing compensatory reactions of the gastric mucosa to the atrophy. Complete regeneration of the gastric mucosa to its previously normal state has never been observed without treatment. The atrophic changes in the cases of more severe involvement either remain stationary or progress.

Jones, Benedict and Hampton [1] were the first to observe and describe apparently complete regeneration of the gastric mucosa after liver therapy in a case of atrophic gastritis associated with pernicious anemia. As seen gastroscopically, the mucosa reassumed its normal thickness, the characteristic gray was replaced by the normal orange-red, the blood vessels of the submucosa became invisible and the entire gastric mucosa was indistinguishable from the normal. This important observation later was confirmed by Chevallier and Moutier,[2] by Lehmann,[3] by Schiff and Goodman,[4] by Schindler [5] and by Schindler and Serby.[6] The last two authors emphasized the fact that the apparent regeneration does not occur in all cases of treated pernicious anemia, for they observed lack of improvement and even progression of the atrophy despite energetic treatment.

Chevallier and Moutier [2] probably were the first to describe cases of atrophic gastritis without pernicious anemia in which the same result, i. e. apparent regeneration of the atrophic mucosa after liver therapy, was obtained. A similar case was reported by Schindler and Serby,[6] who suggested that in some cases atrophic gastritis may be the result of a lack of the antianemic factor without concomitant changes in the blood and also that a parallelism between atrophy of the tongue, of the pharynx and of the stomach and changes in the cord should be assumed. Furthermore, Chevallier and Moutier [2] found that atrophic gastritis was present in some cases of hypochromic anemia and that in several of these the atrophic changes disappeared after iron therapy. This observation has been recently confirmed by Schiff.

The evidence seems to indicate, therefore, that atrophic gastritis, in some cases at least, is related to a deficiency state.

There is no available information to indicate whether this apparently complete regeneration, as seen gastroscopically, is a true histologic regeneration. There have been no microscopic studies in cases in which the gastric mucosa became normal after liver therapy. It is to be hoped that such observations will be made in the future. Brown found in cases of treated pernicious anemia that the gastric mucosa examined at necropsy

1. Jones, C. M.; Benedict, E. B., and Hampton, A. O.: Variations in Gastric Mucosa in Pernicious Anemia, Am. J. M. Sc. **190**:596, 1935.

2. Chevallier, P., and Moutier, F.: La gastroscopie dans les maladies du sang, Sang **11**:935, 1937.

3. Lehmann, R.: Les atrophies gastriques dans les anémies idiopathiques et les métanémies, Paris, E. François, 1936.

4. Schiff, L., and Goodman, S.: Chronic Gastritis: Present Day Status, Ohio State M. J. **34**:1220, 1938.

5. Schindler, R.: Gastroscopy: The Endoscopic Study of Gastric Pathology, Chicago, University of Chicago Press, 1937.

6. Schindler, R., and Serby, A. M.: Gastroscopic Observations in Pernicious Anemia, Arch. Int. Med. **63**:334 (Feb.) 1939.

showed no changes from the usual appearance associated with the untreated disease. It is possible that in these cases no regeneration would have been seen at gastroscopic examination. However, the fact remains that the living gastric mucosa in cases in which there has been a response to sufficient treatment cannot be distinguished from a normal mucosa. This observation has led us to employ systematic substitution therapy in 8 cases of atrophic gastritis not associated with pernicious anemia, combined cord degeneration, sprue or pellagra. Only cases were chosen in which the gastroscopic appearance was marked and in which repeated gastroscopic examinations were possible. The developments in case 1 are reported as control observations in a case of untreated atrophic gastritis. In the subsequent 8 cases, to be presented briefly, the effect of substitution therapy on the gastroscopic picture alone is given chief emphasis. The clinical reaction to this treatment will not be described, since spontaneous remissions of symptoms, sometimes of long duration, are frequent in this disease. Cases 2, 3 and 4 are instances of severe atrophic gastritis in which substitution therapy was unsuccessful. In cases 5 to 8 liver therapy led to the apparent regeneration of the gastric mucosa previously described. In case 9 liver therapy was unsuccessful, while treatment with iron was followed by mucosal regeneration.

REPORT OF CASES

CASE 1.—*Atrophic gastritis not treated with substitution therapy.*

A 66 year old Irish woman was first seen on Oct. 4, 1937, with the complaints of epigastric pain and marked weakness of ten to fifteen years' duration. Her condition had been diagnosed elsewhere as gastric ulcer, although no ulcer was demonstrated on roentgen examination. Her pain usually was relieved by warm liquids; the relief from alkalis was only temporary. At the time of examination she was thin and appeared weak. The thyroid gland was enlarged and nodular, but otherwise the examination gave negative results.

Gastric analysis after an Ewald test meal showed free hydrochloric acid and total acidity 32. The histamine test, with 0.5 mg., showed free hydrochloric acid 28. The stools did not contain any occult blood.

The hemoglobin content was 79 per cent, and the red blood cell count 4,710,000.

Roentgenograms showed that the gallbladder, esophagus and stomach were normal but that there were two diverticula of the second portion of the duodenum.

The course of the disease was characterized by remissions and relapses of symptoms. In December 1937 the patient stated that she had not felt better in many years. In June 1938, however, her symptoms recurred.

Gastroscopic examination on Oct. 22, 1937, disclosed that in the midportion and the upper portion of the stomach the mucosa was thinned and gray and contained some blood vessels. The impression of atrophic gastritis of the upper portions of the lesser curvature and anterior wall was given. On June 24, 1938, in the midportion of the stomach extensive atrophy was seen involving the lesser curvature.

the anterior wall and the greater curvature. The mucosa was gray and appeared thinner than normal. Patchy atrophic areas were observed in the upper portion of the stomach.

The impression was of atrophic gastritis of the upper portions of the stomach.

This was a typical case of atrophic gastritis not treated by substitution therapy. Gastroscopic check eight months after the initial gastroscopic examination showed no essential change in the mucosa, although the patient improved clinically with a bland diet and sedatives.

CASE 2.—*Atrophic gastritis not influenced by liver therapy.*

A 56 year old Italian man was first seen on July 21, 1937, complaining of gas, belching and a salty bitter taste in his mouth, all of three years' duration; he also complained of having had substernal and epigastric pain for four to five months. He had lived chiefly on bread and milk for two years; the epigastric pain, however, was not related to the taking of food. His condition had been diagnosed elsewhere as gastric ulcer and gallbladder disease. The physical examination gave essentially negative results.

Gastric analysis after an Ewald test meal showed free hydrochloric acid 0 and total acidity 6. Two histamine tests, each with 0.5 mg. (Nov. 3, 1937, and Feb. 19, 1938), revealed no free hydrochloric acid. The hemoglobin content varied between 84 and 92 per cent and the red blood cell count between 4,560,000 and 5,000,000.

Roentgenograms revealed a normal gallbladder, esophagus, stomach and duodenum.

From Nov. 13 to Dec. 31, 1937, the patient received at approximately weekly intervals intramuscular injections of Lederle's liver extract [7] in 1 cc. amounts for a total of 8 cc. On Nov. 3, 1937, gastroscopic examination disclosed that the antrum and the pylorus were normal. Above the musculus sphincter antri the mucosa of the anterior wall was thin and gray and the blood vessels were visible. Patchy areas of redness with adherent mucus were seen in the highest portion of the stomach. The impression gained was of atrophic gastritis of the anterior wall of the body of the stomach and mild chronic superficial gastritis of the fornix of the stomach. At gastroscopic examination on Jan. 1, 1938, the antrum and the pylorus appeared normal. The mucosa of the body, especially of the anterior wall, of the greater curvature and of the posterior wall, was thin and gray and contained an extensive network of branching blood vessels. Patches of adherent mucus were observed in the highest portions of the stomach. The impression gained was of chronic superficial and atrophic gastritis. The atrophic gastritis became more extensive, and no effect of the liver therapy was noted.

The atrophic gastritis in this case did not respond to liver therapy; in fact the condition became more extensive.

CASE 3.—*Atrophic gastritis not influenced either by iron therapy or by liver therapy.*

A 44 year old white sheet metal worker when admitted to the hospital on April 28, 1937, stated that for eighteen months he had experienced attacks of epigastric pain for periods of two weeks followed by short remissions. The pain occurred usually two to four hours after meals and was relieved by food or powders. He had lost 18 pounds (8.2 Kg.) during this time. In addition, he

7. The concentrated extract was used.

complained of having had soreness under the right costal border associated with nausea for four years. He had been weak and dizzy for two weeks prior to his admission. Physical examination gave negative results except to reveal tenderness in the epigastrium.

Gastric analysis after an Ewald test meal (May 4, 1937) and two histamine tests, each with 0.5 mg. (June 12, 1937, and July 2, 1938), revealed no free hydrochloric acid. The stools contained no occult blood. The blood count on seven occasions was normal.

Roentgenograms revealed that the esophagus, stomach, duodenum and gallbladder were normal. The clinical course was uneventful. The patient's improvement began on June 12, 1937, and continued until July 10, 1938, although he did not receive specific substitution therapy during this period. However, he stated that he felt particularly well after receiving liver therapy. Seven gastroscopic examinations were performed. Between the third and fourth observations (Aug. 8 and Sept. 9, 1937) the patient received 0.8 Gm. of ferrous sulfate daily. Between the fourth and sixth examinations (Sept. 22, 1937, and Jan. 15, 1938) he received at weekly intervals fifteen intramuscular injections, each of 1 cc. of Lederle's liver extract. Additional liver extract was given at two week intervals from Jan. 28 to May 4, 1938 in 1 cc. amounts, until a total of 6 cc. was given.

On June 2, 1937, the mucosa of the antrum, the anterior wall and the lesser curvature of the body of the stomach presented pinkish nodes. Several gray patches, apparently thinned mucosa, were seen below the cardia; one of these contained small red blood vessels. An impression of diffuse chronic gastritis and beginning atrophy in the upper portions of the stomach was received. On June 23 the nodes had disappeared, but thin gray mucosa with visible blood vessels was observed in the highest portion of the stomach, which gave the impression of atrophic gastritis. On August 11 large areas of thin gray mucosa with blood vessels were visible in the body of the stomach, giving an impression of progressive atrophic gastritis. After this examination, iron therapy, as previously mentioned, was started. On September 10 large portions of the lesser curvature and of the fornix presented a thin smooth gray mucosa containing a net of blood vessels, which gave the impression of extensive atrophic gastritis with further progression in spite of the iron therapy. The administration of iron therefore was discontinued and liver therapy instituted. On November 24 the atrophic gastritis was unchanged. On Feb. 18, 1938, there was extensive atrophic gastritis with visualization of thick blue blood vessels. One small grayish yellow erosion was noted in the anterior wall. No liver therapy was given for two months prior to the examination on July 29, 1938, at which time the greater curvature of the antrum, the entire anterior wall and the lesser curvature of the stomach were completely atrophic. Only scattered portions of the posterior wall still presented a normal mucosa.

In this case the progression of atrophic gastritis over a period of fifteen months was observed in a total of seven gastroscopic examinations. It is obvious that neither iron nor liver therapy had any marked effect on the condition of the gastric mucosa.

CASE 4.—*Atrophic gastritis not influenced by liver, ascorbic acid, nicotinic acid or vitamins.*

A 53 year old laborer when first seen, on June 1, 1938, stated that he had been markedly weak and fatigued and had lost his appetite after a tonsillectomy performed in February 1938. The physical examination gave negative results except to reveal the usual physical signs of bronchial asthma.

The hemoglobin content of the blood varied from 70 to 90 per cent and the red cell count from 4,140,000 to 4,800,000. No occult blood was found in the stools. Gastric analysis after an Ewald test meal on June 10 and a histamine test, with 0.5 mg., on June 13, showed no free hydrochloric acid. However, histamine tests, each with 0.6 mg., on July 27 and 29 and August 12 revealed, respectively, 32, 38 and 30 units of free hydrochloric acid. Histamine tests, with 0.6 mg., on September 3 and 18 again showed no free hydrochloric acid. Histamine tests, with 0.6 mg., on Oct. 3 and 28, 1938, and March 8, 1939, demonstrated 20, 28 and 24 units of free hydrochloric acid, respectively. . Roentgenograms were entirely normal.

On June 20, 1938, the entire gastric mucosa was swollen and nodular. Two superficial ulcerations were visible. On July 11 the nodule formation was less marked. A section of the middle portion of the lesser curvature was depressed and thinned and presented two bluish blood vessels. On July 25 many nodes were still visible. Large portions of the body of the stomach were atrophic, thin and gray. The diagnosis of rapidly progressive hyperplastic atrophic gastritis was made. By August 1 no proliferative hyperplastic changes were visible. Extensive atrophic areas were present in the lesser curvature, in the anterior wall and in the lower portion of the greater curvature. The impression gained was of diffuse atrophy of inflammatory origin. Up to this time the patient had been treated simply with a high caloric, bland diet. After this examination he received ascorbic acid, 0.025 Gm. daily from August 1 to August 11 and 0.10 Gm. daily from August 11 to September 2. On August 10 the mucosa of the antrum looked fairly normal. The atrophic changes of the body were unaltered. One week later extensive atrophy of the gastric mucosa was again observed. On August 31 the mucosa of the antrum and posterior wall appeared edematous and contained collections of adherent mucus. The atrophic changes of the body were still present. Administration of ascorbic acid now was discontinued. From September 2 to 19 the patient received daily intramuscular injections of Lederle's liver extract in 1 cc. amounts until a total of 17 cc. was reached. On September 8 extensive atrophic gastritis was seen, and it was unchanged by September 16. At this point liver therapy was discontinued, and the patient next received 0.10 Gm. of nicotinic acid daily. By September 26 the picture had changed entirely. Unusually severe superficial gastritis was present. The mucosa was edematous and diffusely reddened, and there were extensive layers of adherent mucus. The atrophic areas were covered by this mucus, and it was considered that a superficial inflammation was superimposed on an atrophic mucosa. During the week preceding this examination the patient complained of increased weakness, so the administration of nicotinic acid was discontinued. On October 12 examination showed that the severe superficial gastritis had disappeared and only atrophy of the mucosa was present. On October 31 there was again extensive atrophic gastritis. The atrophic gastritis was more marked two weeks later, and vitamins in the form of "ABD capsules" were given twice daily. Unfortunately the patient was required to undergo a bilateral radical sinus operation, and for a time no gastroscopic examinations could be made. The administration of vitamins was discontinued from December 9 to 13 but was then resumed. On Feb. 1, 1939, a spectacular improvement was noted. The mucosa of the antrum appeared slightly thinner than normal, but the severe atrophic changes of the body of the stomach had disappeared almost completely. Only a small area, in the midportion of the lesser curvature, presented several extremely small gray patches containing red blood vessels. An examination on March 9 revealed recurrence of extensive atrophy despite the administration of vitamins in reduced doses.

This report is only preliminary. The case was of great interest, because we were able to witness the development and progression of

severe atrophic gastritis at regular and frequent gastroscopic examinations. Attempts to influence the atrophic gastritis by giving the patient liver extract, ascorbic acid and nicotinic acid were in vain. A spectacular improvement was noted during therapy with a mixture of vitamins. In this period of improvement, a radical nasal sinus operation was performed, but it seemed unlikely that the elimination of foci of infection could lead to the regeneration of atrophic gastric mucosa. It was possible that this improvement was coincidental, since the atrophy recurred while vitamin therapy was continued. However, the doses of vitamins, prior to the last gastroscopic examination had been reduced to one half the original amount. This patient is being observed carefully, and a more complete study will be reported later.

CASE 5.—*Spectacular improvement of atrophic gastritis following liver therapy and recurrence after discontinuation of treatment.*

A 64 year old German laborer was hospitalized on Aug. 16, 1938, because of an old depressed skull fracture. He also had experienced, for several years, severe colicky pain in the upper part of the abdomen one or two hours after meals. The pain was relieved by vomiting. Treatment for ulcers at another institution had been ineffective. The physical examination gave negative results except to disclose a depression of the left frontal region of the skull.

A histamine test on August 21 with 0.75 mg. and on November 17 with 0.68 mg. showed complete anacidity. A third histamine test, on Jan. 11, 1939, with 0.69 mg., revealed 10 units of free hydrochloric acid after forty minutes. No occult blood was found in the stools. Five blood counts were normal. Roentgenologic examination demonstrated a very small diaphragmatic herniation of the stomach. The esophagus, duodenum, colon and gallbladder were normal.

Six gastroscopic examinations were performed. After the second, intramuscular injections of 2 cc. of Lederle's liver extract were given for seventeen days (October 12 to 29), the patient receiving a total of 12 cc. A second course of liver therapy was administered between the fifth and sixth gastroscopic examinations, the patient receiving 1 cc. weekly (Jan. 25 to March 8, 1939) until a total of 6 cc. was reached.

On Aug. 29, 1938, gastroscopic examination showed that the pylorus and the antrum were normal. The mucosa of the anterior wall was thinned with a gray admixture. There was a protrusion of the posterior wall, covered with nodes and gray-whitish areas, which, however, became flatter by inflation of air. The mucosa of the posterior wall and the greater curvature above this protrusion was somewhat stiff and bumpy and presented grayish areas between the elevations. In the highest level the gastric mucosa was thinned and pinkish gray and contained many blood vessels. An impression of severe hyperplastic atrophic gastritis was gained. On October 12 some nodes were still seen but the prominence of the posterior wall had disappeared. Almost the entire body of the stomach was atrophic. The impression given was of extensive atrophic gastritis. On November 14 two definite gray spots on the anterior wall were the only remnants of the previously severe atrophic gastritis. This showed spectacular improvement of atrophic gastritis with liver therapy. On December 14 gastroscopic examination revealed a small area of atrophy above the angulus. On Jan. 25, 1939, the mucosa of the antrum was slightly atrophic. The mucosa of the greater curvature and the posterior wall of the midportions of the stomach were so thin that blood vessels were visible. There

were fresh hemorrhages in the atrophic mucosa of the posterior wall. This showed that the atrophic gastritis had become worse again.

Spectacular improvement of extensive atrophic gastritis apparently followed the first course of liver therapy, although slight areas of atrophy still were visible. The original picture reappeared after discontinuation of the liver therapy. There was no improvement after the second course of such therapy, however, and further study is required to evaluate its effectiveness in this case. The case is of interest because of the appearance of free hydrochloric acid after liver therapy, suggesting, perhaps, a true regeneration of functionally active glandular structures in the stomach, even though this improvement was temporary.

CASE 6.—*Atrophic gastritis disappearing after liver therapy but reappearing after the discontinuation of this treatment.*

This case has been reported elsewhere and is therefore summarized briefly here. A 49 year old white American housewife had complained of rather generalized abdominal distress for twenty-five years. She suffered from marked fatigue and nervousness. The physical examination gave essentially negative results. She was observed from Jan. 27, 1932, until June 24, 1936.

Gastric analysis after an Ewald test meal and three histamine tests, each with 0.5 mg., revealed no free hydrochloric acid. There was no occult blood in the stools. Frequent blood counts were normal. All roentgenologic examinations gave negative results. Four gastroscopic examinations were performed. After the second the patient received intramuscular injections of 1 cc. of Lederle's liver extract until a total of 25 cc. was given (April 13 to Sept. 12, 1936).

Gastroscopic examination on July 12, 1935, revealed severe atrophic gastritis of the body of the stomach (diffuse thinning with visible red and blue blood vessels). On March 24, 1936, there was extensive atrophic hemorrhagic gastritis extending from the angulus to the cardia. Liver therapy was instituted after this examination. On June 15 in the midportion of the anterior wall there were two pinpoint hemorrhagic areas. Otherwise the gastric mucosa looked normal. Liver therapy was continued until September 12, when the patient voluntarily discontinued it. Examination on October 28 revealed patchy gray areas on the anterior and posterior wall, which were more extensive in the highest portions of the stomach. The changes, however, were less pronounced than those seen at the first gastroscopic examination.

This was our first case of marked atrophic gastritis in which an apparent improvement was observed following liver therapy. This, it seemed to us, was a remarkable therapeutic result, the significance of which was further emphasized by the reappearance of the typical gastroscopic signs of atrophic gastritis after the patient discontinued treatment.

CASE 7.—*Extensive atrophic gastritis with marked improvement following liver therapy.*

A 42 year old American saleswoman had had a diagnosis of psychoneurosis with secondary depression. The possible relation between her emotional problems and the atrophic gastritis will not be considered. She entered the hospital on July 11, 1938, because of intermittent dull aching pain in the epigastrium of ten years' duration and sharp epigastric pain of six weeks' duration occurring two hours after

meals. This pain was relieved by food, usually milk; alkalis gave only temporary relief. The physical examination gave negative results.

Three histamine tests, each with 0.6 mg., indicated complete anacidity. The stools contained no blood. Three blood counts were normal. Roentgenograms of the gastrointestinal tract also were normal. Four gastroscopic examinations were performed. Between the third and fourth the patient received, within one month (August 29 to September 22), 4 cc. of Lederle's liver extract intramuscularly in divided doses.

On July 14 the mucosa of the lower part of the posterior wall looked smooth but mottled; circular dark red mucosal hemorrhages were seen in this region. Marked changes were seen in the midportions of the stomach: the thin gray smooth mucosa contained fine red blood vessels. Branching blue blood vessels were noted in the highest portions of the lesser curvature. The impression of extensive atrophic hemorrhagic gastritis was received. On August 5 there were extensive atrophic areas on the midportion and upper portion of the stomach. Two weeks later scattered patches of mucus were present in the antrum. One gray atrophic patch was observed in the angulus (i. e., much lower than the changes seen at the previous examination). The atrophic changes of the midportion and upper portion of the stomach were unaltered. Liver extract was then administered, as mentioned previously. On November 2 the picture had changed so much that it was hardly recognizable. No atrophy and no blood vessels were seen. The number of highlights was perhaps still slightly increased, but the atrophic changes, if still present, were amazingly reduced since the last examination.

We have never before observed such spontaneous improvement of severe atrophic gastritis, although the senior author has observed several cases of severe involvement over a number of years. Three gastroscopic examinations before institution of liver therapy showed no improvement in this case and serve therefore as control observations. The sudden disappearance of the atrophy following the brief period of liver therapy suggests a specific therapeutic result.

CASE 8.—*Marked improvement of atrophic gastritis following liver therapy.*

This case is reported very briefly because the gastroscopic observations were exceedingly difficult owing to a lack of cooperation on the part of the patient. A 34 year old American housewife had received various forms of treatment, including liver therapy, for persistent anemia; no liver therapy, however, had been given since 1935. Her chief complaints were epigastric tenderness and weakness. The physical examination gave essentially negative results.

The hemoglobin content from Sept. 11, 1933 to Feb. 6, 1939, varied between 74 and 82 per cent and the red blood cell count between 3,700,000 and 4,810,000. A special hematologic examination showed no evidence of pernicious anemia. Three histamine tests, with 0.3 mg. and 0.4 mg., revealed 10 to 48 units of free hydrochloric acid. Roentgenologic examinations gave negative results. Gastroscopic examinations were performed on July 30, 1938, and Feb. 6, 1939. Between these examinations the patient received a total of 16 cc. of Lederle's liver extract intramuscularly.

On July 23, 1938, gastroscopic examination revealed that the mucosa of the antrum was slightly gray. Small grayish patches were seen in the anterior wall above the angulus. These changes became more marked and larger toward the cardia, and large areas of smooth pinkish gray mucosa with small red blood vessels

and a few large blue blood vessels were seen in the fornix. A beanlike prominence (inflammatory polyp) was seen in the midportion of the lesser curvature. An impression of extensive atrophic gastritis of almost the entire stomach was gained. The liver therapy followed this examination. On Feb. 6, 1939, gastroscopic examination showed that the antrum was normal. The atrophic changes had diminished markedly. The mucosa was still slightly thinned in the lower portions of the lesser curvature and the anterior wall.

A definite improvement of the atrophic gastritis in this case followed liver therapy. It should be noted here that anacidity is proved by histamine tests in only one third of all cases of atrophic gastritis. This case demonstrates that free hydrochloric acid may be present despite extensive atrophy of the gastric mucosa.

CASE 9.—*Apparent healing of atrophic gastritis following iron therapy in a case of hypochromic anemia.*

A 43 year old Jewish housewife was seen originally by her local physician in May 1938 because of marked fatigue, which in November 1938 bordered on exhaustion. She had been treated for anemia by injections of liver extract. She was first seen at Albert Merritt Billings Hospital on Dec. 20, 1938, still complaining of marked fatigue.

An examination of the blood revealed a hemoglobin content of 35 per cent and a red cell count of 3,670,000. Study of a stained blood smear revealed moderate anisocytosis and a number of polychromatophilic cells. Gastric analysis after an Ewald test meal and two histamine tests, with 0.61 mg. on Jan. 3 and 0.64 mg. on Feb. 2, 1939, indicated complete anacidity. Roentgenologic studies gave normal results. Iron therapy (0.2 Gm. of ferrous sulfate five times daily) was started immediately after the first gastroscopic examination, on Dec. 30, 1938. The patient improved in a short time, although she continued to feel somewhat tired. The hemoglobin content rose to 80 per cent and the red blood cell count to 4,570,000.

Gastroscopic examination on Dec. 30, 1938, revealed that the mucosa of the body of the stomach was markedly atrophic. Large areas were seen in which the mucosa appeared to be thin and gray and contained large nets of blood vessels. This gave an impression of extensive atrophic gastritis. It might be mentioned at this point that atrophy and pallor cannot be confused gastroscopically as each gives its own characteristic picture. The two are often observed together in pernicious anemia. On Feb. 6, 1939, a tiny gray area containing a blood vessel was seen in the midportion of the stomach. All the other atrophic changes seen previously had disappeared, and the gastric mucosa appeared entirely normal. There was spectacular, almost complete, healing of the atrophic gastritis following iron therapy.

Apparent healing of atrophic gastritis following iron therapy has been described by Chevallier and Moutier [2] and by Schiff and Goodman.[4] This is the first case in which we have been able to make the same observation.

COMMENT

In evaluating the effectiveness of specific therapeutic measures, a thorough knowledge of the natural history of the disease is imperative. The senior author has observed a sufficient number of cases of untreated

atrophic gastritis to warrant the statement that severe atrophic gastritis does not completely disappear spontaneously. This impression is confirmed by the findings in case 1 and the control observations in cases 4, 5 and 6. Despite this previous experience, we feel that by studying the natural evolution of the disease in many more cases, the danger of attributing specific curative effects to perhaps only coincidental results, such as occurred in case 4, will be avoided.

It is obvious from this preliminary report that in many cases atrophic gastritis does not respond to specific substitution treatment. In other cases the improvement is temporary. Whether or not these results indicate causes of atrophic gastritis other than a deficiency state is chiefly speculative. On the other hand, the findings in cases 6 to 9 suggest a deficiency factor and, furthermore, justify the continued use of specific substitution therapy. The mechanism of the action of iron and liver in changing the appearance of the mucosa in iron deficiency anemia and pernicious anemia is as yet completely unknown.

SUMMARY

The effect of substitution therapy on the course of atrophic gastritis, as witnessed by gastroscopic examination in 8 cases, is described in a preliminary report.

Liver therapy was ineffective in case 2, and liver and iron therapy was ineffective in case 3. In case 4 the condition was unaffected by liver, ascorbic acid and nicotinic acid and probably by vitamins. In cases 5 to 8 the gastric mucosa became apparently normal after liver therapy. When this treatment was interrupted, the atrophy reappeared in 2 cases. Iron therapy was apparently successful in case 9.

It is impossible in the present state of knowledge to say whether or not the apparent regeneration of the gastric mucosa is genuine, i. e., due to the formation of new glands. Microscopic studies are necessary to solve this question.

The use of substitution therapy, such as the administration of liver, iron or vitamins, is justified in the treatment of atrophic gastritis as an approach to clarifying the nature and pathogenesis of this condition. It must be emphasized that control studies, prolonged observation and competent interpretation of findings are necessary before evaluation of such therapy is possible.

VITAMIN A DEFICIENCY IN DIABETES MELLITUS

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The occurrence of increased amounts of carotene in the blood of patients with diabetes mellitus has long been recognized both by the clinical observation of xanthosis and by the results of laboratory tests. As early as 1904 von Noorden and Isaac [1] commented on the yellow pigmentation occurring in some patients with diabetes mellitus. In 1914 Palmer and Eckles [2] showed that carotene was present in the blood in the form of a carotoalbumin, and in 1919 Hess and Myers [3] correlated the occurrence of increased amounts of carotene in the blood with the yellowish pigmentation of the skin previously noted by von Noorden. In 1929 and 1930 Rabinowitch [4] noted that in patients with diabetes mellitus and xanthosis the diabetes appeared to be more severe and more difficult to control than in those without hypercarotenemia. In 85 per cent of 500 cases of diabetes mellitus studied at that time the carotene values were above normal. Later Rabinowitch [5] stated that for some unknown reason patients with diabetes mellitus tend to retain vegetable pigments more than do patients without diabetes and that this accounts for the high incidence of hypercarotenemia among persons with diabetes.

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White and Gordon,[6] using a modification of Palmer's [7] method for determining the amount of carotene in the blood, studied the values for carotene in the blood of normal persons and of patients with diabetes mellitus and observed that the normal range was from 2 to 8 dichromate units. In patients with diabetes mellitus the values ranged from 5 to 25 dichromate units, averaging 14 units. Later studies by Stueck, Flaum and Ralli [8] reported the average amount to be 26 dichromate units in patients with diabetes mellitus.

Drummond, Gilding and MacWalter [9] injected carotene into the saphenous vein of cats and noted that it was rapidly absorbed by the reticuloendothelial system. The greatest concentration was in the Kupffer cells of the liver. A slight amount was found in the lungs and in the spleen.

Ralli, Brandaleone and Mandelbaum [10] in 1935 and Ralli, Pariente and Brandaleone [11] in 1936 gave diets with the same carotene content to a group of patients with diabetes mellitus and to a group of normal persons. The patients with diabetes mellitus had higher initial blood carotene levels than did the normal group, and the content increased more rapidly with the high carotene diet and fell more slowly when that diet was discontinued than in the normal group. This study, coupled with determinations of the carotene content of the livers of diabetic patients who came to autopsy, led to a possible explanation of the high values of carotene in the blood of patients with diabetes mellitus. It was believed that this high value was a result of the inability of the livers to convert carotene to vitamin A, resulting in an accumulation of carotene in the blood stream. The cholesterol content of the blood of control persons averaged 173 mg. per hundred cubic centimeters, and that of patients with diabetes mellitus, 203 mg. per hundred cubic centimeters.

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Heymann [12] reported similar feeding experiments with a normal group and with a group of patients with diabetes mellitus. He also observed higher initial values of carotene in the blood of patients with diabetes mellitus than in that of the normal group. When equivalent amounts of carotene were fed to the two groups, the values for carotene increased more rapidly, reached higher levels and tended to remain elevated for a longer period of time after the diet was discontinued in the diabetic than in the normal group. It was felt that this was not due to the accompanying hypercholesteremia or hyperglycemia.

Clausen [13] in 1933 found that the vitamin A content of the liver of a patient with diabetes mellitus studied at autopsy was low. Jeghers [14] in 1937, while studying various types of diseases, reported that the liver is the main storage depot of vitamin A and that it regulates the concentration of vitamin A throughout the body. Moore [15] in 1937 observed that the reserves of vitamin A were above normal in the livers of patients with diabetes mellitus who had come to autopsy and suggested that the high level tends to rule out the theory that the liver of the diabetic person is unable to convert carotene to vitamin A. He stated the belief that both carotene and vitamin A accumulate in patients with diabetes mellitus because of a general slowing down of the metabolism of the body.

In 1938 Bessey and Wolbach [16] postulated that the carotene content of the plasma is a measure of the difference between the rate of absorption from the intestines and the rate of conversion into vitamin A and also that the rate of conversion is diminished in patients with diabetes mellitus and with certain diseases of the liver.

The foregoing studies have suggested several explanations, which are somewhat at variance, for the relation between the amount of carotene and that of vitamin A in the blood of patients with diabetes mellitus. If one is to accept Ralli's [11] explanation that the increased amount of carotene, is due to an inability of the liver of a patient with diabetes mellitus to convert carotene to vitamin A, it would seem to follow that a state of vitamin A deficiency might well tend to develop in

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such a patient in spite of an adequate intake of carotene. The proof of the occurrence of night blindness, clinical or subclinical, or other evidence of the presence of vitamin A deficiency in a group of patients with diabetes mellitus might well tend to substantiate this suggested paradox of vitamin A deficiency in the face of the high carotene content of the blood.

The biophotometric determination of early vitamin A deficiency suggested a means of studying this problem in patients with diabetes mellitus. Jeghers,[14] using the biophotometer in a study of diseases of the liver, reported among his control groups 1 case of diabetes mellitus in which the biophotometer reading was below normal. Later Feldman [17] tested a series of 8 patients with diabetes mellitus by means of the adaptometer and noted that 4 of the 8 showed evidence of dysadaptation.

With all these facts in mind the following study was undertaken.

METHOD

With a Frober-Faybor biophotometer and according to the methods outlined by Jeans, Blanchard and Zentmire [18] and by Jeghers,[19] a series of 20 interns and staff members of the University Hospital were tested by the same observer under like conditions, and the results were tabulated and checked. Readings in the experiments were recorded in milli-foot-candles instead of as direct biophotometer readings. In each case readings were made at the following times: (1) on entering the dark room, (2) after a ten minute period in the dark, (3) twenty seconds after a three minute period of bleaching, (4) after three minutes of recovery, (5) after six minutes of recovery and, finally, (6) after ten minutes of recovery.

All members of the control group ate a diet which had a minimum vitamin A content of 4,000 U. S. P. units per day. The average biophotometric curve for the group was determined and compared with Jegher's [19] "low normal" curve. The cholesterol content of the blood was determined in each instance by Sackett's [20] modification of Bloor's [21] method. The carotene content was determined by White and Gordon's [6] modification of Palmer's [7] method and expressed as dichromate units.

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A series of ambulatory young and early middle-aged patients, presenting either the classic history and clinical picture of diabetes mellitus or the definitely abnormal dextrose tolerance curves of the diabetic type, or both, were studied. All these patients had a type of diabetes which occurs in youth or in early middle life and is commonly called the juvenile type of diabetes mellitus. Each member of the group was studied in a manner similar to that employed for the control group. In addition, each was observed clinically for evidence of cutaneous changes suggestive of vitamin A deficiency and questioned regarding subjective evidence of night blindness.

All patients had their diabetes either controlled or in the process of being controlled during the study. Some showed glycosuria, but none had any clinical or laboratory signs of acidosis. All patients had ophthalmoscopic examinations by a competent ophthalmologist, and only those with normal fundi are reported on here. All biophotometric readings were made two hours postprandially.

A group of 7 patients with diabetes mellitus with subnormal biophotometer readings was given a daily supplement of 8 cc. of carotene in vegetable oil,[22] containing 60,000 U. S. P. units of vitamin A, in divided doses for periods of seven days. Two patients in this group received the daily supplement for a period of fourteen days. In both groups biophotometric readings and determinations of cholesterol and carotene in the blood were obtained before and after the periods of supplementary feeding.

Twenty patients with diabetes mellitus were given a concentrated fish liver oil,[23] containing approximately 60,000 U. S. P. units of vitamin A, as a daily supplement for periods ranging from three to twenty-one days. Biophotometer readings and blood cholesterol and blood carotene values were determined before and after the periods of supplementary feeding, and the results were tabulated and charted.

In order to show that the results were not coincidental, associated with "learning" or due to improvement in the diabetic status, the routine was varied in two ways: (1) by feeding the vitamin A supplement before the carotene supplement in a portion of the cases and (2) by depriving the group of the vitamin A supplement that had previously maintained normal or near normal biophotometer readings and then retesting them after short periods without the supplement.

RESULTS

The numerical readings for the control group shown in table 1 are expressed graphically in figure 1. It is to be noted that the reading twenty seconds after the bleaching exceeded the twenty second value reported by Jeghers,[19] 0.74 milli-foot-candle, and the one reported by Corlette, Youmans, Frank and Corlette,[24] 0.7 milli-foot-candle, in 10 cases, but in no instance did it exceed the low borderline reading of

22. Smaco carotene in vegetable oil (1 cc. contains 7,500 U. S. P. units of vitamin A).

23. Parke, Davis haliver oil capsules, "Natola" (1 capsule contains approximately 9,800 U. S. P. units of vitamin A).

24. Corlette, M. B.; Youmans, J. B.; Frank, H., and Corlette, M. G.: Photometric Studies of Visual Adaptation in Relation to Mild Vitamin A Deficiency in Adults, Am. J. M. Sc. **195**:54 (Jan.) 1938.

1 milli-foot-candle given by Jeans, Blanchard and Zentmire.[18] The readings after three, six and ten minutes of recovery were all well within the normal recovery range as advocated by Jeghers.[14] An average of the twenty sets of readings was established as the average normal reading for our biophotometer under the given conditions. The blood carotene values for normal persons (table 1) ran higher than the previously reported observations, possibly because the subjects tested had slightly more than an adequate amount of carotene in the diet. The average cholesterol value, of 200 mg. per hundred cubic centimeters (table 1), agreed fairly well with what is generally considered the upper normal limit.

A study of table 2 reveals the fact that all the readings taken after twenty seconds of recovery were lower than the lowest limit of borderline normal readings noted by Jeans, Blanchard and Zentmire,[18] and all were much lower than any of those for the control subjects. None of the twenty sets of readings in the periods three and six minutes after bleaching equaled those of the control group, and the values for only 3 of the 20 patients (1, 8 and 16) fell into the range between our normal average and Jeghers'[19] low normal value (table 1). Three patients (5, 11 and 15) presented values within normal limits in one of the periods but not in both. The carotene values, as expected, were higher than normal in 90 per cent of the cases studied (table 2), averaging 23 dichromate units, in contrast to an average of 13 dichromate units for the control group. Of the 2 patients having low carotene values (5 and 18), 1 was markedly emaciated on admission, and the factor of low intake of carotene might have played a role in the determination. The other patient had been on a low fat diet for a considerable time before the experiment. Cholesterol values varied widely, from 154 to 342 mg. per hundred cubic centimeters of blood, but the average was approximately 39 mg. greater in the patients with diabetes. The scatter graph (fig. 2) graphically portrays the difference between the individual and the average readings for the diabetic patients and our average normal readings.

Clinically, of 20 patients studied in table 2, 3 gave a history of night blindness and 9 showed keratosis pilaris, which is described as one of the manifestations of vitamin A deficiency.[16]

A group of 7 patients with diabetes mellitus was given crystalline carotene dissolved in vegetable oil, 60,000 U. S. P. units of vitamin A, daily for seven days. Table 3 shows that there was relatively little change in the readings before and after the supplement. Slight improvement was noted in the reading after twenty seconds of recovery for patients 2, 3 and 6; but in no case did the readings approach normal

TABLE 1.—*Biophotometer Readings for Twenty Supposedly Normal Males, with the Simultaneously Determined Values of Carotene and Cholesterol in the Blood*

Patient	Initial Reading in Dark Room, Milli-Foot-Candles	After 10 Minute Dark Period, Milli-Foot-Candles	Light	20 Seconds After 3 Minute Bleach, Milli-Foot-Candles	3 Minute Recovery, Milli-Foot-Candles	6 Minute Recovery, Milli-Foot-Candles	10 Minute Recovery, Milli-Foot-Candles	Blood Carotene, Dichromate Units	Blood Cholesterol, Mg. per 100 Cc.
1	0.18	0.01		1.00	0.11	0.03	0.01	17	276
2	0.92	0.18		0.63	0.08	0.03	0.01	14	...
3	0.24	0.10		0.26	0.10	0.08	0.04	12	208
4	0.63	0.12		0.44	0.08	0.08	0.05	12	194
5	0.69	0.14		0.58	0.16	0.05	0.02	15	248
6	0.76	0.11		0.84	0.15	0.09	0.02	..	186
7	0.58	0.06		0.92	0.14	0.06	0.03	10	205
8	0.92	0.08		0.58	0.15	0.09	0.02	12	188
9	0.47	0.05		0.92	0.14	0.06	0.05	16	177
10	0.58	0.14		0.76	0.14	0.07	0.03	15	230
11	0.24	0.02		0.58	0.11	0.05	0.02	14	202
12	0.63	0.08		0.69	0.15	0.08	0.03	14	192
13	0.84	0.04		0.92	0.19	0.06	0.03	12	182
14	0.84	0.04		0.63	0.11	0.06	0.03	16	178
15	0.47	0.03		1.00	0.22	0.05	0.03	14	233
16	0.63	0.07		0.92	0.16	0.06	0.02	14	206
17	0.47	0.05		0.84	0.16	0.05	0.03	14	156
18	0.84	0.10		0.84	0.26	0.12	0.05	12	147
19	0.63	0.07		0.92	0.22	0.11	0.04	14	222
20	0.58	0.03		0.69	0.16	0.04	0.02	12	176
Average normal	0.61	0.07		0.75	0.15	0.07	0.03	13	200
Jegher's low normal	0.80	0.28		0.74	0.32	0.14	0.10		

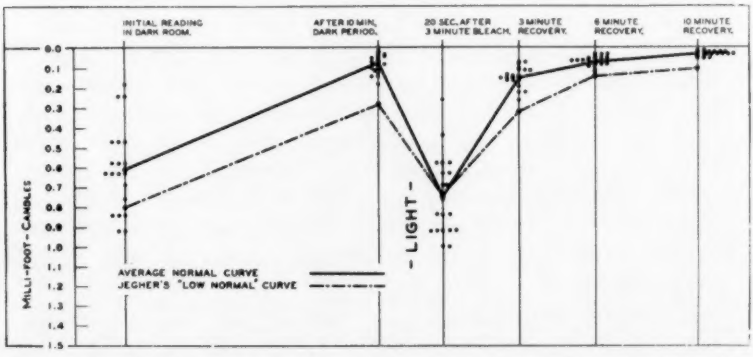

Fig. 1.—Frequency distribution of determinations on normal males (table 1). The average normal curve is compared with Jegher's low normal curve.

figures. The conditions in the remainder of the patients were unchanged or became worse while they received the carotene supplement during the seven and fourteen day periods. Normal readings after three and six minutes of recovery were noted in 1 instance (patient 2), and slight improvement was noted in patient 3. The remaining 5 patients showed

TABLE 2.—*Biophotometer Readings for Twenty Persons with Juvenile Diabetes (with Normal Fundi), Compared with the Readings for Normal Males (Table 1)*

Patient	Initial Reading in Dark Room, Milli-Foot-Candles	After 10 Minute Dark Period, Milli-Foot-Candles	Light	20 Seconds After 3 Minute Bleach, Milli-Foot-Candles	3 Minute Recovery, Milli-Foot-Candles	6 Minute Recovery, Milli-Foot-Candles	10 Minute Recovery, Milli-Foot-Candles	Blood Carotene, Dichromate Units	Blood Cholesterol, Mg. per 100 Cc.
1	1.36	0.03		1.22	0.26	0.06	0.02	30	342
2	0.92	0.14		1.80	0.35	0.19	0.08	24	250
3	1.22	0.18		2.40	0.76	0.35	0.14	28	210
4	0.84	0.22		1.80	0.35	0.18	0.11	16	168
5	0.44	0.03		1.95	0.44	0.08	0.01	16	250
6	1.36	0.06		1.95	0.47	0.18	0.03	20	216
7	0.58	0.02		1.60	0.38	0.15	0.04	20	229
8	0.35	0.10		1.80	0.29	0.08	0.04	26	198
9	1.00	0.32		1.22	0.38	0.16	0.08	20	260
10	0.69	0.11		1.48	0.38	0.18	0.07	..	250
11	1.22	0.16		1.22	0.35	0.07	0.04	20	330
12	1.95	0.26		1.95	0.84	0.38	0.18	16	176
13	2.40	1.10		2.40	0.69	0.22	0.08	14	154
14	1.22	0.14		1.48	0.52	0.22	0.07	25	230
15	1.60	0.03		1.95	0.35	0.12	0.03	35	236
16	1.48	0.08		1.10	0.26	0.08	0.02	40	...
17	0.44	0.06		2.16	0.44	0.18	0.04	18	306
18	0.76	0.29		2.40	0.38	0.19	0.11	8	283
19	1.10	0.22		2.40	0.84	0.52	0.26	40	234
20	0.92	0.29		1.95	0.84	0.47	0.24	28	220
Average reading	1.05	0.19		1.80	0.48	0.20	0.09	23	239
Normal	0.61	0.07		0.75	0.15	0.07	0.03	13	200
Difference	+0.44	+0.12		+1.05	+0.33	+0.13	+0.06	+10	+39

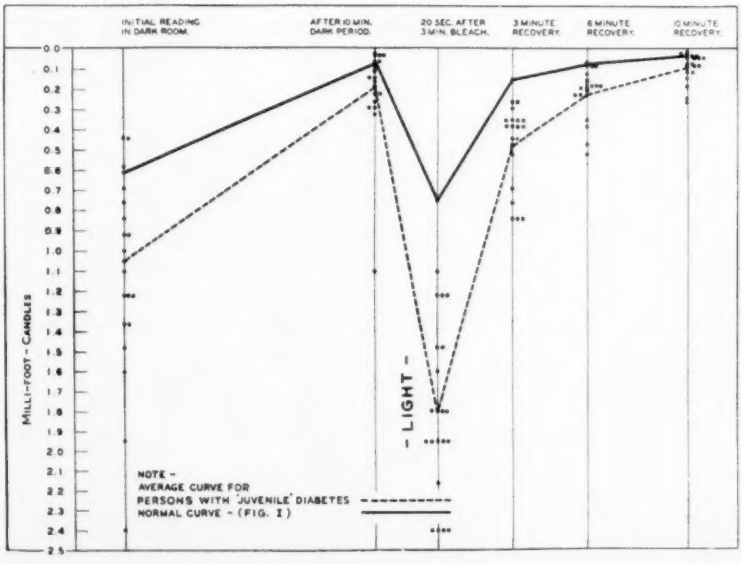

Fig. 2.—Frequency distribution of determinations on persons with juvenile diabetes (table 2). Compare the composite curve with the normal curve (fig. 1).

TABLE 3.—*The Effect on the Biophotometer Readings of Feeding Persons with Juvenile Diabetes 8 Cc. of Carotene in Oil (Approximately 60,000 U. S. P. Units of Vitamin A) per Day as a Supplementary Feeding*

Patient	8 Cc. Carotene in Oil Daily	Initial Reading in Dark Room, Milli-Foot-Candles	After 10 Minute Dark Period, Milli-Foot-Candles	Light	20 Seconds After 3 Minute Bleach, Milli-Foot-Candles	3 Minute Recovery, Milli-Foot-Candles	6 Minute Recovery, Milli-Foot-Candles	10 Minute Recovery, Milli-Foot-Candles	Blood Carotene, Dichromate Units	Blood Cholesterol, Mg. per 100 Cc.
1 A	Before carotene supplement	0.92	0.14		1.80	0.35	0.19	0.08	24	250
B	After carotene 7 days.....	1.48	0.26		1.80	0.58	0.26	0.14	26	208
2 A	Before carotene supplement	0.44	0.03		1.97	0.44	0.06	0.01	10	250
B	After carotene 7 days.....	0.32	0.02		1.22	0.24	0.08	0.02	30	236
3 A	Before carotene supplement	1.10	0.22		2.40	0.84	0.52	0.26	40	234
B	After carotene 7 days.....	1.60	0.19		1.48	0.32	0.19	0.11	40	192
4 A	Before carotene supplement	0.69	0.11		1.48	0.38	0.18	0.07	..	250
B	After carotene 7 days.....	1.60	0.19		1.95	0.63	0.26	0.08	30	210
5 A	Before carotene supplement	1.22	0.14		1.48	0.52	0.22	0.07	25	230
B	After carotene 7 days.....	1.22	0.23		2.16	0.58	0.22	0.14	35	172
6 A	Before carotene supplement	0.84	0.12		1.95	0.47	0.19	0.07	24	240
B	After carotene 7 days.....	1.22	0.09		1.60	0.44	0.16	0.06	25	194
C	After carotene 14 days.....	1.36	0.12		2.40	0.84	0.29	0.10	35	250
7 A	Before carotene supplement	2.40	0.06		2.40	0.76	0.22	0.08	25	212
B	After carotene 7 days.....	2.40	0.06		2.40	0.69	0.26	0.10	40	208
C	After carotene 14 days.....	2.40	0.19		2.40	0.69	0.32	0.11	50	220
	Average for diabetic patients									
	Before supplement.....	1.09	0.12		1.93	0.54	0.23	0.09	25	238
	After 7 day supplement.....	1.41	0.15		1.80	0.54	0.20	0.09	32	203
	Difference.....	+0.32	+0.03		−0.13	0	−0.03	0	+ 7	− 35

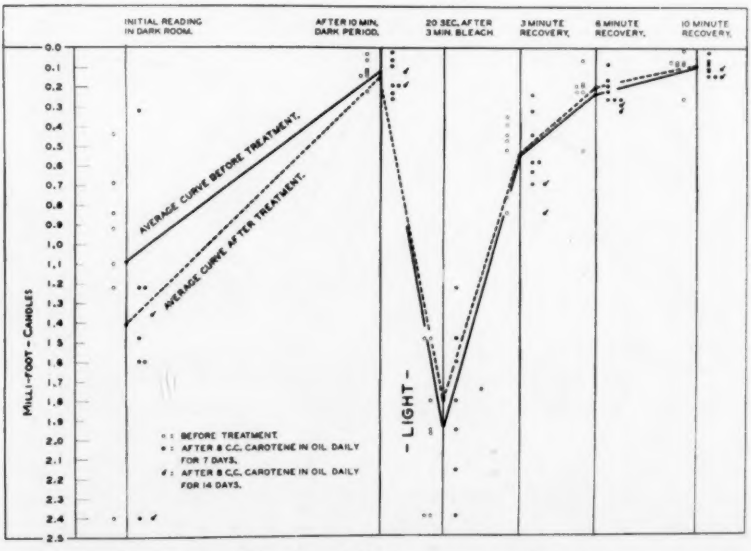
INITIAL READING IN DARK ROOM.
AFTER 10 MIN. DARK PERIOD.
20 SEC. AFTER 3 MIN. BLEACH.
3 MINUTE RECOVERY.
6 MINUTE RECOVERY.
10 MINUTE RECOVERY.
MILLI-FOOT-CANDLES
AVERAGE CURVE BEFORE TREATMENT.
AVERAGE CURVE AFTER TREATMENT.
- LIGHT -
o : BEFORE TREATMENT.
• : AFTER 8 C.C. CAROTENE IN OIL DAILY FOR 7 DAYS.
✓ : AFTER 8 C.C. CAROTENE IN OIL DAILY FOR 14 DAYS.

Fig. 3.—Frequency distribution of biophotometer readings for persons with juvenile diabetes before and after treatment with 8 cc. of carotene in oil daily (table 3).

TABLE 4.—*Biophotometer Readings for Persons with Juvenile Diabetes Before and After Feeding 1.2 Cc. of Halibut Liver Oil Supplement (Approximately 60,000 U. S. P. Units of Vitamin A) per Day for Varying Numbers of Days*

Patient	1.2 Cc. Halibut Liver Oil Daily	Initial Reading in Dark Room, Milli-Foot-Candles	After 10 Minute Dark Period, Milli-Foot-Candles Light	20 Seconds After 3 Minute Bleach, Milli-Foot-Candles	3 Minute Recovery, Milli-Foot-Candles	6 Minute Recovery, Milli-Foot-Candles	10 Minute Recovery, Milli-Foot-Candles	Blood Carotene, Dichromate Units	Blood Cholesterol, Mg. per 100 Cc.
1.	Before supplement	1.60	0.03	1.95	0.35	0.12	0.03	35	236
	After 3 days vitamin A	0.84	0.08	1.10	0.35	0.07	0.06	35	292
	Difference	−0.76	+0.05	−0.85	0	−0.05	+0.03	0	+26
2.	Before supplement	0.92	0.03	1.10	0.35	0.16	0.04	24	260
	After 4 days vitamin A	0.76	0.04	1.00	0.24	0.10	0.03	22	292
3.	Before supplement	0.92	0.10	1.48	0.35	0.14	0.07	30	274
	After 4 days vitamin A	1.00	0.09	0.76	0.22	0.11	0.05	30	244
4.	Before supplement	1.00	0.14	1.10	0.35	0.19	0.09	40	192
	After 4 days vitamin A	1.36	0.05	0.52	0.16	0.07	0.04	40	220
	Average before supplement	0.95	0.09	1.23	0.35	0.16	0.07	31	242
	Average after 4 days vitamin A	1.04	0.06	0.76	0.21	0.09	0.04	31	252
	Difference	+0.09	−0.03	−0.47	−0.14	−0.07	−0.03	0	+10
5.	Before supplement	0.92	0.16	1.36	0.29	0.09	0.05	24	222
	After 5 days vitamin A	0.38	0.08	0.92	0.14	0.08	0.02	30	212
6.	Before supplement	0.44	0.02	1.60	0.14	0.05	0.03	30	216
	After 5 days vitamin A	0.35	0.02	0.58	0.06	0.02	0.01	30	216
	Average before supplement	0.68	0.09	1.48	0.22	0.07	0.04	27	219
	Average after 5 days vitamin A	0.36	0.05	0.80	0.09	0.05	0.01	30	214
	Difference	−0.32	−0.04	−0.68	−0.13	−0.02	−0.03	+3	−5
7.	Before supplement	1.48	0.08	1.10	0.26	0.08	0.02	40	...
	After 6 days vitamin A	1.10	0.16	0.76	0.26	0.15	0.02	40	...
8.	Before supplement	0.44	0.06	2.16	0.44	0.18	0.04	18	306
	After 6 days vitamin A	0.58	0.12	0.76	0.08	0.03	0.02	20	230
	Average before supplement	0.96	0.07	1.63	0.35	0.13	0.03	29	...
	Average after 6 days vitamin A	0.83	0.14	0.76	0.17	0.09	0.02	30	...
	Difference	−0.13	+0.07	−0.87	−0.18	−0.04	−0.01	+1	...
9.	Before supplement	1.22	0.16	1.22	0.35	0.08	0.04	20	330
	After 7 days vitamin A	0.63	0.18	0.52	0.24	0.11	0.08	24	234
10.	Before supplement	1.00	0.32	1.22	0.38	0.16	0.08	20	260
	After 7 days vitamin A	0.76	0.47	1.48	0.38	0.14	0.11	18	210
11.	Before supplement	0.58	0.02	1.60	0.38	0.15	0.04	20	220
	After 7 days vitamin A	0.92	0.09	0.63	0.09	0.04	0.02	25	203
12.	Before supplement	1.60	0.29	1.60	0.58	0.29	0.12	20	250
	After 7 days vitamin A	1.22	0.09	1.00	0.32	0.18	0.11	25	334
13.	Before supplement	0.92	0.10	1.80	0.47	0.19	0.08	34	216
	After 7 days vitamin A	0.76	0.08	1.36	0.38	0.19	0.08	25	234
	Average before supplement	1.06	0.18	1.49	0.43	0.17	0.07	23	257
	Average after 7 days vitamin A	0.86	0.18	1.00	0.28	0.13	0.05	23	263
	Difference	−0.20	0	−0.49	−0.15	−0.04	−0.02	−0	+6
	Average before supplement	1.00	0.12	1.48	0.36	0.14	0.06	26	248
	Average after 3-7 days vitamin A	0.90	0.12	0.88	0.22	0.10	0.05	28	243
	Difference	−0.10	0	−0.60	−0.14	−0.04	−0.01	+2	−5
14.	Before supplement	2.40	0.47	1.80	0.63	0.24	0.12	26	208
	After 8 days vitamin A	1.36	....	1.22	0.35	0.24	....	24	257
15.	Before supplement	0.76	0.20	2.40	0.38	0.19	0.11	8	283
	After 8 days vitamin A	1.36	0.16	0.92	0.19	0.12	0.08	18	252
	Average before supplement	1.58	0.38	2.10	0.51	0.22	0.11	17	245
	Average after 8 days vitamin A	1.36	....	1.07	0.27	0.18	....	18	255
	Difference	−0.22	....	−1.03	−0.24	−0.04	....	+1	+10
16.	Before supplement	2.16	0.26	2.16	0.52	0.32	0.18	28	188
	After 14 days vitamin A	0.84	0.09	1.00	0.24	0.16	0.05	24	148

TABLE 4.—*Biophotometer Readings for Persons with Juvenile Diabetes Before and After Feeding 1.2 Cc. of Halibut Liver Oil Supplement (Approximately 60,000 U. S. P. Units of Vitamin A) per Day for Varying Numbers of Days—Continued*

Patient 1.2 Cc. Halibut Liver Oil Daily	Initial Reading in Dark Room, Milli-Foot-Candles	After 10 Minute Dark Period, Milli-Foot-Candles Light	20 Seconds After 3 Minute Bleach, Milli-Foot-Candles	3 Minute Recovery, Milli-Foot-Candles	6 Minute Recovery, Milli-Foot-Candles	10 Minute Recovery, Milli-Foot-Candles	Blood Carotene, Dichromate Units	Blood Cholesterol, Mg. per 100 Cc.
17. Before supplement	1.95	0.32	2.16	0.92	0.38	0.18	16	176
After 14 days vitamin A	0.58	0.09	0.44	0.16	0.05	0.01	18	214
Average before supplement	2.06	0.29	2.16	0.72	0.35	0.18	22	181
Average after 14 days vitamin A	0.71	0.09	0.72	0.20	0.11	0.03	21	181
Difference	−1.35	−0.20	−1.44	−0.52	−0.44	−0.15	−1	0
18. Before supplement	0.63	0.08	1.22	0.32	0.08	0.03	20	256
After 15 days vitamin A	0.92	0.07	0.63	0.11	0.05	0.02	20	274
Difference	+0.29	−0.01	−0.59	−0.21	−0.03	−0.01	0	+18
19. Before supplement	2.16	0.26	2.40	1.36	0.69	0.12	15	166
After 15 days vitamin A	0.92	0.08	1.10	0.22	0.07	0.02	12	154
Difference	−1.24	−0.18	−1.30	−1.14	−0.62	−0.10	−3	−12
20. Before supplement	0.84	0.15	1.60	0.38	0.29	0.06	22	214
After 21 days vitamin A	1.48	0.44	1.95	0.58	0.19	0.09	24	228
Difference	+0.64	+0.29	+0.35	+0.20	−0.10	+0.03	+2	+14
Average before supplement	1.56	0.26	1.96	0.64	0.31	0.11	19	213
Average after 8-21 days vitamin A	1.07	0.16	1.04	0.26	0.13	0.05	19	218
Difference	−0.49	−0.13	−0.92	−0.38	−0.18	−0.06	0	+5
Grand average								
Before supplement	1.20	0.17	1.65	0.46	0.21	0.08	25	236
After 3-21 days vitamin A	0.91	0.13	0.93	0.24	0.11	0.05	25	235
Difference	−0.29	−0.04	−0.72	−0.22	−0.10	−0.03	0	−1

no significant improvement, and the average for the group after carotene supplements were added to the diet showed little change from that before the giving of the supplements. An increase in the carotene content of the blood was noted for 5 of the 7 patients. Patient 3 had a high value throughout the study. The general trend of the cholesterol values after the addition of a carotene supplement to the diet was slightly downward but not consistently so. Figure 3 graphically portrays the lack of beneficial effect of feeding the carotene supplements.

Table 4 shows that of the 13 patients who received 60,000 U. S. P. units of vitamin A daily in the form of fish liver oil for intervals of three to seven days, 12 showed improvement in the reading taken twenty seconds after bleaching. Of these 12, 7 had normal values (0.75 milli-foot-candle or less) and 4 close to normal (1 to 0.75 milli-foot-candle), and 1 had a slightly improved value. The thirteenth patient, no. 10, showed a slightly lower reading after the carotene supplement than before. Three and six minutes after recovery significant improvement was noted in 11 of the 13 patients, with slight improvement in the

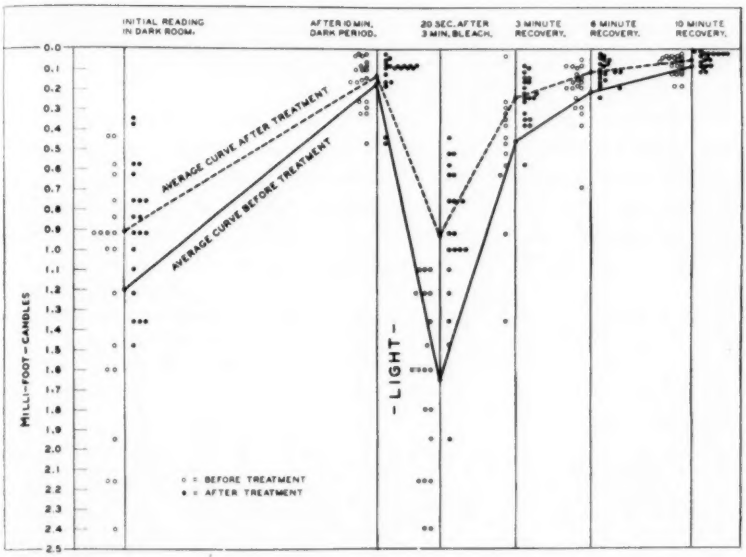

Fig. 4.—Frequency distribution of biophotometer readings for diabetic young persons before and after treatment with halibut liver oil supplement equivalent to 60,000 U. S. P. units of vitamin A daily.

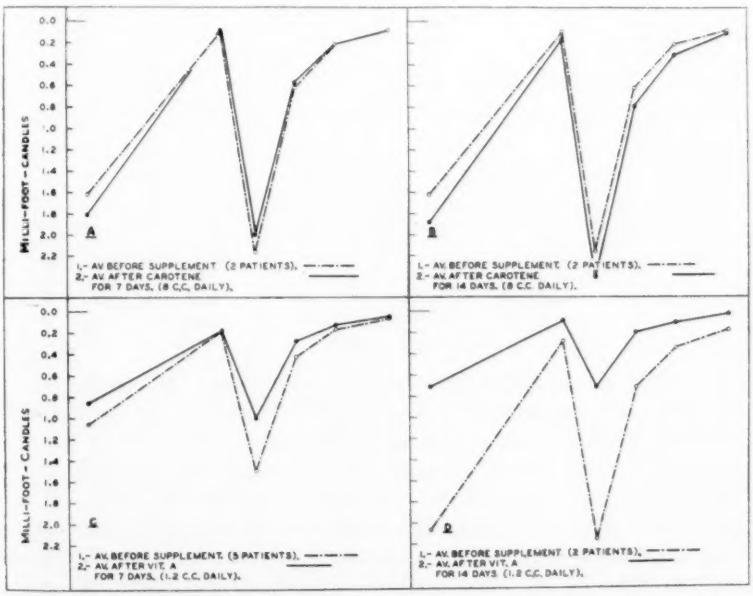
MILLI-FOOT-CANDLES
A
1.- AV. BEFORE SUPPLEMENT (2 PATIENTS).
2.- AV. AFTER CAROTENE FOR 7 DAYS. (8 C.C. DAILY).
B
1.- AV. BEFORE SUPPLEMENT (2 PATIENTS).
2.- AV. AFTER CAROTENE FOR 14 DAYS. (8 C.C. DAILY).
C
1.- AV. BEFORE SUPPLEMENT (5 PATIENTS).
2.- AV. AFTER VIT. A FOR 7 DAYS. (1.2 C.C. DAILY).
D
1.- AV. BEFORE SUPPLEMENT (2 PATIENTS).
2.- AV. AFTER VIT. A FOR 14 DAYS. (1.2 C.C. DAILY).

Fig. 5.—Comparison of the effect of carotene and vitamin A administered for periods of seven and fourteen days.

remaining 20. In the patients that received vitamin A for eight to twenty-one days the results were similar to those obtained with the shorter period of administration.

Figure 4 graphically depicts the changes, including average curves before and after the fish oil supplement. There was relatively little change in the carotene and cholesterol values during this phase of the experiment. That there was no difference in the resultant effects of

TABLE 5.—*The Effect of Removing Vitamin A Supplement from Diabetic Patients Whose Biophotometer Readings Had Been Previously Maintained at Normal or Slightly Subnormal Levels by the Vitamin A Supplement*

Patient		60,000 U.S.P. Units of Vitamin A Daily	Initial Reading in Dark Room, Milli-Foot-Candles	After 10 Minute Dark Period, Milli-Foot-Candles Light	20 Seconds After 3 Minute Bleach, Milli-Foot-Candles	3 Minute Recovery, Milli-Foot-Candles	6 Minute Recovery, Milli-Foot-Candles	10 Minute Recovery, Milli-Foot-Candles	Blood Carotene, Dichromate Units	Blood Cholesterol, Mg. per 100 Cc.
1	A	For 4 days	1.00	0.09	0.76	0.22	0.11	0.05	30	244
	B	None for 5 days	0.84	0.12	1.22	0.28	0.14	0.09	25	236
2	A	For 5 days	0.35	0.02	0.58	0.03	0.02	0.01	30	212
	B	None for 6 days	0.84	0.12	1.95	0.47	0.19	0.07	24	240
3	A	For 7 days	0.92	0.09	0.63	0.09	0.04	0.02	25	203
	B	None for 6 days	0.84	0.03	0.92	0.19	0.08	0.03	30	234
4	A	For 34 days	0.84	0.09	1.00	0.24	0.16	0.05	22	148
	B	None for 7 days	2.40	0.38	2.40	0.76	0.22	0.08	25	212
5	A	For 5 days	0.35	0.02	0.58	0.03	0.02	0.01	30	216
	B	None for 12 days	0.32	0.02	1.00	0.08	0.04	0.02	30	180
6	A	For 7 days	0.76	0.08	1.36	0.38	0.19	0.08	25	234
	B	None for 14 days	1.10	0.14	1.95	0.52	0.18	0.08	16	156
7	A	For 4 days	1.36	0.05	0.52	0.16	0.07	0.04	40	220
	B	None for 20 days	1.00	0.08	1.48	0.29	0.12	0.04	40	176
8	A	For 30 days	1.10	0.11	0.92	0.24	0.11	0.06	12	154
	B	None for 20 days	1.80	0.14	1.95	0.52	0.19	0.05	10	221
9	A	For 6 days	0.58	0.12	0.76	0.08	0.03	0.02	40	...
	B	None for 24 days	1.48	0.32	1.95	0.63	0.26	0.03	30	...
10	A	For 14 days	0.58	0.09	0.38	0.16	0.05	0.01	18	214
	B	None for 35 days	2.16	0.29	1.22	0.32	0.08	0.06	20	197
11	A	For 15 days	0.92	0.70	0.63	0.11	0.05	0.02	20	274
	B	None for 5 months	2.40	0.76	2.40	0.92	0.58	0.44	28	258
		Average with supplement	0.80	0.08	0.74	0.16	0.06	0.03	27	212
		Average with no supplement	1.38	0.22	1.68	0.45	0.19	0.09	25	211
		Difference	+0.58	+0.14	+0.94	+0.29	+0.11	+0.06	−2	−1

administering the supplements over periods of fourteen days rather than seven days is shown graphically by figure 5; there was improvement with supplements of vitamin A but not with carotene.

The effect of removing vitamin A supplements from patients with diabetes mellitus whose biophotometer readings had previously been maintained at normal or nearly normal levels by means of the supplements is shown in table 5. After twenty seconds of recovery, in 9 of the 11 cases the values became significantly abnormal after discontinuance of the supplements and in the remaining 2 cases they showed

drops to the borderline level. After three and six minutes of recovery the values in 6 of the 11 cases dropped to markedly abnormal levels after discontinuance of the supplements, and the values in the remaining 5 cases dropped to lower but not abnormal levels. The result certainly seems to show that the previously noted improvement while the patients were receiving vitamin A supplements was due to the supplements themselves and not to coincidence or "learning" factors. Figure 6 graphically depicts these changes, with average curves before and after the use of the supplements was discontinued. No significant changes were noted in the values for cholesterol or carotene.

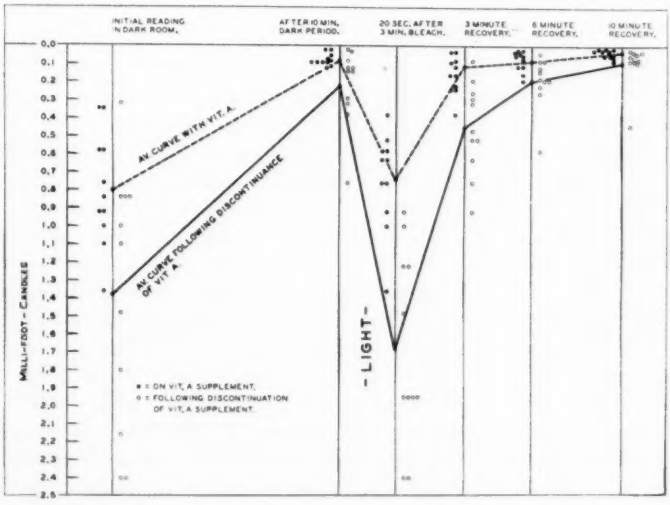

Fig. 6.—The effect on biophotometer readings of removing vitamin A supplement from diabetic patients whose biophotometer readings had been maintained at normal or slightly subnormal levels by the supplement.

COMMENT

In connection with the previously mentioned observations the following work is of interest: Jeghers [19] in 1937 placed normal subjects on diets containing 200 U. S. P. units of vitamin A daily and in six days obtained lower biophotometer readings. After thirty-one days of the diet, improvement was noted twenty minutes after the patient was given an oral dose of 80,000 U. S. P. units of vitamin A, and the curves became normal after three days of feeding 100,000 units per day. Jeghers [19] also reported that patients with diseased livers did not respond to carotene, but the administration of vitamin A resulted in

improved readings. Wald, Jeghers and Arminio [25] in 1938, using the "adaptometer," noted that subjects deficient in vitamin A because of dietary restrictions responded to 100,000 U. S. P. units of vitamin A by mouth in thirty minutes and to a similar amount of carotene in thirty-eight minutes. Smaller doses, of 17,000 U. S. P. units of vitamin A and 20,000 units of carotene, gave similar results. It is of interest to note that patients treated in this way became hemeralopic two days after they discontinued taking the 100,000 unit doses of the supplement.

Although only 3 of our 20 patients studied were subjectively aware of night blindness, the biophotometer readings were all in a range compatible with some degree of night blindness.

SUMMARY

A control group of 20 subjects gave biophotometer readings comparable to the normal values obtained by other observers. Twenty patients with diabetes mellitus but with normal fundi who were tested in like manner by the same observer had biophotometer readings definitely suggestive of vitamin A deficiency in spite of blood carotene levels consistently above normal. Three of the group presented a history of night blindness, and 9 showed clinical evidence of mild vitamin A deficiency by cutaneous changes. Large doses of carotene for an adequate period failed to improve the biophotometer readings significantly in spite of increasing the already high blood carotene values. Comparable amounts of vitamin A given over similar periods produced significant improvement in the biophotometer readings. Removal of the vitamin A supplement from the diet of patients whose readings were held normal or nearly normal by the supplement resulted in immediate relapse to subnormal values. In this respect the patients reacted similarly to those studied by Wald, Jeghers and Arminio,[25] their conditions relapsing promptly after the discontinuance of the large doses of vitamin A. The values for carotene in 90 per cent of the patients with diabetes mellitus studied were above normal. No definite correlation was noted between the blood cholesterol values and the changes induced during the course of the experiment.

CONCLUSIONS

A group of 20 patients with juvenile diabetes mellitus were studied, and all were found to have poor light adaptation by the Frober-Faybor biophotometer. Three of the group were subjectively aware of night blindness, and 9 showed cutaneous changes compatible with vitamin A deficiency.

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25. Wald, G. H.; Jeghers, H., and Arminio, J.: Experiment in Human Dietary Night Blindness, Am. J. Physiol. **123**:732 (Sept.) 1938.

The daily administration of 60,000 U. S. P. units of vitamin A, in the form of crystalline carotene dissolved in vegetable oil, for as long as fourteen days did not affect the light adaptation of the patients with diabetes mellitus.

The daily administration of 60,000 U. S. P. units of vitamin A to patients with diabetes mellitus, in the form of concentrated fish liver oils, caused their light adaptation to return to normal or nearly normal in periods ranging from three to twenty-one days.

The cause of poor light adaptation in patients with juvenile diabetes mellitus appears to be an inability to convert carotene to vitamin A.

SYNDROME OF PSEUDOBULBAR PALSY

AN ANATOMIC AND PHYSIOLOGIC ANALYSIS

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Pseudobulbar palsy is a syndrome about which little is known in spite of the fact that it not uncommonly follows cerebral vascular accidents and other forms of neurologic disease. It is our purpose, therefore, to present an anatomic and physiologic analysis of this condition.

Magnus [1] first reported a case in which there were features characteristic of pseudobulbar palsy following multiple apoplectic attacks; he discussed the postmortem observations. Jolly [2] described a patient with multiple sclerosis and "progressive bulbar paralysis" whose bulbar nuclei were normal at autopsy; Barlow [3] emphasized the relation of bilateral cortical lesions to the syndrome. Ross [4] reviewed cases from an anatomic-functional point of view, and Oppenheim and Siemerling [5] differentiated pseudobulbar from true bulbar palsy. Hunter and Robertson [6] and Oettinger [7] reported typical cases.

GENERAL CONSIDERATIONS

The designation "pseudobulbar palsy" is a misnomer. The term supranuclear bulbar paralysis would be more accurate. This term indicates the general position of the lesion and makes clear the distinction

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1. Magnus, A.: Fall von Aufhebung des Willenseinflusses auf einige Hirnnerven, Arch. f. Anat., Physiol. u. wissensch. Med., 1837, p. 258.

2. Jolly, F.: Klinische Mittheilungen über einige in Folge des Feldzugs von 1870-1871 entstandene Psychosen, Arch. f. Psychiat. **3**:442, 1872.

3. Barlow, T.: On a Case of Double Hemiplegia, with Cerebral Symmetrical Lesions, Brit. M. J. **2**:103, 1877.

4. Ross, J.: Labio-Glosso-Pharyngeal Paralysis of Cerebral Origin, Brain **5**:145, 1882.

5. Oppenheim, H., and Siemerling, E.: Die acute Bulbärparalyse und die Pseudobulbärparalyse, Berl. klin. Wchnschr. **23**:791, 1886; abstracted, Charité-Ann. **12**:331, 1887.

6. Hunter, W. K., and Robertson, M. E.: A Case of Pseudobulbar Paralysis, Rev. Neurol. & Psychiat. **10**:101, 1912.

7. Oettinger, B.: A Case of Pseudobulbar Paralysis, Presenting Facial Spastic Movements Simulating Laughter, M. Rec. **84**:737, 1913.

between nuclear and central types of paralysis. However, the term pseudobulbar palsy is firmly entrenched in the literature.

Pseudobulbar palsy must be considered in relation to other causes of weakness of the bulbar muscles. These muscles may be paralyzed owing to disease involving the muscles themselves, their connections with the motor nuclei of the brain stem or their supranuclear control by the higher centers. Thus, myasthenia gravis appears to be primarily a disease of muscle. Progressive muscular atrophy and syphilitic basilar meningitis attack the lower motor neurons, causing secondary degeneration of the muscles and true bulbar palsy. Finally, bilateral injury of pathways from the cerebral motor cortex controlling the bulbar nuclei gives rise to the syndrome of pseudobulbar palsy.

It is evident that various factors may give rise to the lesions. Moreover, the corticobulbar fibers may be attacked at different points along their course. The anatomic changes, which must be bilateral, may occur in the cerebral motor cortices, the internal capsules, the cerebral peduncles or the pons.

The cardinal clinical features on which the diagnosis is based are grouped under difficulties of speech, difficulties of mastication and difficulties of deglutition, without signs of injury of the bulbar nuclei. Levy [8] noticed that there is frequently intellectual enfeeblement. Loss of emotional control, manifested as forced laughing or crying, appears in typical cases, but the face in repose shows poverty of expression, sadness being the predominating note. Saliva may drip from the mouth; the jaw jerk is hyperactive. The patients eat slowly, owing to difficulties in mastication. The symptoms may come on suddenly or gradually; the rate of onset influences the clinical picture.

The corticospinal as well as the corticobulbar fibers are usually damaged, according to Tilney and Morrison,[9] and quadriplegia results. Less often the extremities are affected unilaterally or in sequence. In certain cases the arms and legs are used fairly well, but even in such cases there are difficulties of coordination in the limbs and the patients walk with short steps.

UNILATERAL INJURY OF CORTICOBULBAR FIBERS

Unilateral interruption of the corticobulbar tract is usually associated with damage to the whole group of efferent fibers from the motor cortex. Loss of function in the bulbar muscles is slight and tends to be transient,

8. Levy, S.: Les troubles de la parole au cours des états pseudobulbaires, Rev. neurol. **2**:289, 1930.

9. Tilney, F., and Morrison, J. F.: Pseuedobulbar Palsy, Clinically and Pathologically Considered, with the Clinical Report of Five Cases, J. Nerv. & Ment. Dis. **39**:505, 1912.

since the nuclei of the cranial nerves are placed under the influence of both motor cortices by commissural neurons.

Immediately after a cerebral vascular accident the eyes may be turned toward the sound side of the body so that it is impossible for the patient to look voluntarily toward the paralyzed side. However, if the gaze is fixed on an object and the head rotated passively, the eyes may be brought to the hemiplegic side. This deviation is demonstrable only for a few days; thereafter the eyes move well in all directions. For the same period the pupil is often larger on the paralyzed side.

Mastication is little impaired by unilateral injury of the corticobulbar fibers. On palpation of the contracting muscles a few days after the vascular accident some weakness may be noticed. When the patient opens the mouth widely there may be deviation of the jaw to the paralyzed side due to loss of strength in the pterygoid muscles on that side.

In hemiplegia the facial muscles show considerable paralysis. For the first few days after the onset these muscles often manifest a complete loss of tone and strength. It is impossible to close the eye tightly, and no resistance is offered to passive raising of the upper lid. The cheek blows in and out with respiration. The facial folds are smoothed on the paralyzed side. Later there is considerable return of function, particularly in the upper part of the face, as the muscles of this region appear to receive a greater degree of bilateral cortical innervation. Although tone is decreased in the facial muscles after the development of hemiplegia, it later returns and may be increased in the paretic muscles, so that the facial folds may be deeper than on the normal side.

The emotional responses of the facial muscles are integrated at a subcortical level; the exact centers and pathways are not yet known. Patients with loss of voluntary facial movement may respond to emotional stimuli on the paralyzed side even more markedly than on the normal.

The pharyngeal and laryngeal muscles show little loss of voluntary function in the presence of unilateral damage to the corticobulbar fibers. During the period of shock the voice may be weak and husky; later it is normal. The soft palate may move more strongly on the normal side, and as a result the uvula may be pulled to that side.

There is permanent weakness of the tongue in some hemiplegic patients. When this is present, the tongue deviates toward the paretic side.

BILATERAL INJURY OF THE CORTICOBULBAR FIBERS

As an example, one may consider a patient with cerebral vascular disease in whom hemiplegia developed first on one side and then on the other. He is examined after the period of shock has passed.

The pupils may or may not be equal in size; they are often small. Movements of the eyes are possible in all directions but are of limited range. There is difficulty in looking upward or in bringing the eyes far to the side. Usually accommodation is lost. The muscles of mastication contract weakly. The jaw jerk is hyperactive. The bilateral facial palsy is usually more marked in the lower portion; it is often possible to wrinkle the forehead slightly and to close the eyes.

Weakness of the pharynx and larynx gives rise to difficulties in swallowing and speaking. If the pseudobulbar palsy develops suddenly after a vascular occlusion, the difficulties of deglutition are particularly marked. In many instances the patient has to be tube fed for days. When the shock decreases, some power of deglutition returns. In case the pseudobulbar palsy develops gradually, the patient escapes complete loss of the power to swallow. Even so, he tends to choke easily. It is difficult to expel mucus from the pharynx; saliva tends to run from the corners of the mouth. Observation of the soft palate or the vocal cords reveals weakness of voluntary movement. Speech is often incomprehensible. The tongue can be protruded only a short distance.

BROADBENT'S HYPOTHESIS

Broadbent [10] developed a hypothesis to explain the varying degree of paralysis of the muscles on the hemiplegic side. He noticed that all of the facial muscles show some degree of paralysis but that function is never entirely lost. There is slight paresis of the muscles of the forehead. For the first few days the orbicularis oculi muscle is obviously weak. The eye on the hemiplegic side cannot be closed independently, and voluntary contraction is less forceful on this side. In the perioral region the paralysis is most marked. The orbicularis oris muscle is less affected than are the straight muscles inserted in the lips and in the angles of the mouth. Perfect closure of the mouth is still possible.

Similarly, the masticatory, lingual and abdominal muscles show incomplete paralysis. The muscles with the mildest degree of weakness are those of the eye, neck, back and chest. The muscles with greatest loss of function are those the usual action of which is independent of the corresponding muscles on the opposite side of the body. The least paretic muscles are those which act only in unison with the contralateral group. In the case of symmetrically acting musculature it seems that the activating neurons have complete commissural connections whereby

10. Broadbent, W. H.: An Attempt to Remove the Difficulties Attending the Application of Dr. Carpenter's Theory of the Function of the Sensori-Motor Ganglia to the Common Form of Hemiplegia, Brit. & For. Med.-Chir. Rev. **37**:468, 1866; A Lecture on the Theory of Construction of the Nervous System, Brit. M. J. **1**:371, 401 and 433, 1876.

the coordination of bilateral muscular function is facilitated. This combination of neurons receives fibers from both motor cortices. It is usually activated by both cortices but is capable of excitation by either singly. Bilateral muscular response is more or less complete depending on whether the commissural connection is more or less perfect.

Observation of patients with almost complete destruction of both corticobulbar tracts shows that an astonishing amount of movement often is possible in the eyes, neck and trunk. This leads to consideration whether there is not a greater subcortical control of movement than is now suspected. The control of motor functions by the cerebral cortex becomes predominant only in the higher apes and in man. Other mammals show mild degrees of paralysis after removal of the motor cortices. Certainly essential activities, such as respiration, maintain efficient function without mediation of the higher centers.

EXPERIMENTAL PRODUCTION IN CATS OF A CONDITION RESEMBLING PSEUDOBULBAR PALSY

It is important to demonstrate that the difficulties of speech and swallowing, together with the loss of emotional control, result from bilateral damage to the corticobulbar tracts. This fact is not universally accepted. In cats a condition, which we consider similar to pseudobulbar palsy, has been produced by bilateral removal of the motor and premotor cerebral cortex (Langworthy and Kolb[11]). It was found that electrical stimulation of the most lateral portion of the anterior cruciate gyrus gave rise to rhythmic chewing and lapping movements. When this area was removed on both sides, the cats showed abnormalities of feeding and emotional disturbances.

The animals at first made no effort to eat spontaneously. If a piece of meat was placed in the mouth and the jaw held closed, chewing movements began. The meat would eventually be swallowed if it was pushed far back in the pharynx. After three or four days the animals began to eat without assistance. They would snatch at food greedily until the whole mouth was filled and then swallow without chewing. Eating initiated emotional reactions manifested usually by loud purring but sometimes by growling.

The difficulties of drinking were more marked than those of eating and persisted for a longer time. On the first day after the operation it was customary to feed the cats from a spoon. Once the milk was introduced into the mouth, swallowing occurred. Lapping movements of the tongue often developed; these showed perseveration and usually continued when feeding was stopped. After two or three days the cats

11. Langworthy, O. R., and Kolb, L. C.: The Experimental Production in the Cat of a Condition Simulating Pseudobulbar Palsy, Am. J. Physiol. **111**:57, 1935.

would make unsuccessful attempts to drink from a dish. They insisted on putting their paws into the fluid. Some opened and closed the mouth and attempted to drink without using the tongue. Lapping became reestablished only after ten days to two weeks, and even then coordination of lapping, swallowing and breathing was abnormal. Often the cats would bite on the glass rim or continue the lapping movements away from the milk or outside the dish. At times they would stand rigid in one position and stare fixedly into space for considerable periods. This appeared to be a cataleptic phenomenon.

PHYSIOLOGIC ANALYSIS OF THE SYMPTOMS OF PSEUDOBULBAR PALSY

The abnormalities associated with pseudobulbar palsy may be classified under the headings of shock, loss of function and release of function. The difficulties in swallowing are certainly more marked immediately after the apoplectic onset of the syndrome, persist for the first few days and then slowly ameliorate; this is a manifestation of shock. There are always some difficulty of deglutition and poor coordination of swallowing with breathing. This signifies a loss of function. The abnormal emotional responses may be taken as an example of release of function.

1. *Swallowing.*—Swallowing is coordinated largely at a reflex level in cases of pseudobulbar palsy. Beevor [12] described the case of a man who was unable to open his mouth voluntarily to admit food. A physician sat at the foot of the bed and went through the motions of yawning, initiating a reflex of similar activity in the patient. When the latter's mouth was open, the nurse inserted food.

Because of the weakness of the pharyngeal muscles, the patients have difficulty in expelling the mucus which tends to collect in the throat. The coordination between breathing and swallowing is poor, so that food may enter the bronchi and cause bronchopneumonia. Since the patients do not swallow readily, saliva accumulates and drips from the mouth.

2. *Speech.*—During the period of shock speaking is impossible. Later the speech disturbances are of many types. Phonation is always poor because of weakness of the articulating muscles due to loss of function. The mechanism of release may sometimes be observed as increased tone in the laryngeal muscles and may manifest itself as a lack of flexibility in sound production. With a slow onset of pseudobulbar palsy, such as is seen in multiple sclerosis, speech is more severely affected than is swallowing. Secondary involvement of other pathways in the nervous system tends to modify the speech disturbances. If the syndrome is produced by pontile lesions, the cerebellar pathways as well as the corticobulbar tracts are injured, and a cerebellar type of dysarthria results.

12. Beevor, C. E.: A Case of Pseudobulbar Paralysis with Complete Loss of Voluntary Respiration, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **15**:537, 1907.

Levy [8] pointed out that there is abnormality both in the rhythm and in the timbre of speech. Dissociation between voluntary and automatic speech is manifested as a type of repetition termed palilalia. Loss of the normal chant or melody of language makes the patients speak in short interjections which are more or less indistinct, monotonous and explosive. Speech is pitched in an unusual and difficult register; the patients use short words and speak with abnormal rapidity. There is a tendency to precede any initial vowel with an aspirate. Difficulty is found in pronouncing labial and labiodental sounds. The voice frequently has a nasal quality. When these troubles reach their maximum, anarthria occurs.

Patients with pseudobulbar palsy sometimes show a loss of tone in the palate and absence of the palatal reflexes. Often one or both vocal cords are fixed in partial adduction. The movements of the diaphragm are irregular, jerky contractions being superimposed on the normal rhythm. There is a tendency toward equality of the inspiratory and the expiratory phase. The disturbances in phonation are to be explained in part on the basis of these respiratory factors. In summary, it may be said that patients show varying abnormalities in speech, depending on the amount of strength of voluntary control lost and the condition of increased or decreased tone present in the muscles of speech. After the period of shock has ended, increased tone may appear in the laryngeal and thoracic musculature and may influence articulation even further.

3. *Respiration.*—Jackson [13] in 1895 observed that Cheyne-Stokes respiration is observed frequently in patients with bilateral injury of the corticobulbar tracts. He stated the belief that the respiratory center in the medulla is released from cortical control and overacts to normal blood-borne chemical stimuli in a rhythmic manner. Other observers (Bucy and Case [14]) demonstrated the cortical control of respiratory activity in the dog and in man by delimiting cortical areas where stimulation caused marked deceleration or arrest of respiration.

We have studied and recorded rhythmicity of respiratory excursions in pseudobulbar palsy (Grimmer, Hesser and Langworthy [15]). A typical record is shown in figure 1. Simultaneous pneumograph tracings were taken from each side of the chest; time is recorded in five second intervals. The upstroke indicates inspiration. Drugs, such as coramine

13. Jackson, J. H.: Superior and Subordinate Centers of the Lowest Level, Lancet **1**:476, 1895.

14. Bucy, P. C., and Case, T. J.: Cortical Innervation of Respiratory Movements, J. Nerv. & Ment. Dis. **84**:156, 1936.

15. Grimmer, R. V.; Hesser, F. H., and Langworthy, O. R.: Rhythmic Variation of Respiratory Excursion with Bilateral Injury of Cortical Efferent Fibers, Arch. Neurol. & Psychiat. **42**:862 (Nov.) 1939.

(a 25 per cent solution of pyridine betacarbonic acid diethylamide) or aminophylline (theophylline with ethylene diamine U. S. P.), as well as the administration of oxygen or carbon dioxide, tended to abolish the periodicity in these cases.

4. *Emotional Release.*—The explanations for emotional release giving rise to forced laughing and crying have never been satisfactory; the most logical discussion has been presented by Wilson.[16] Pathologic laughing and crying refer to the manifestation of involuntary and irresistible emotional outbursts as a consequence of cerebral lesions.

The stimuli which arouse the exaggerated, forced, involuntary and uncontrollable laughing or weeping are often inadequate as well as

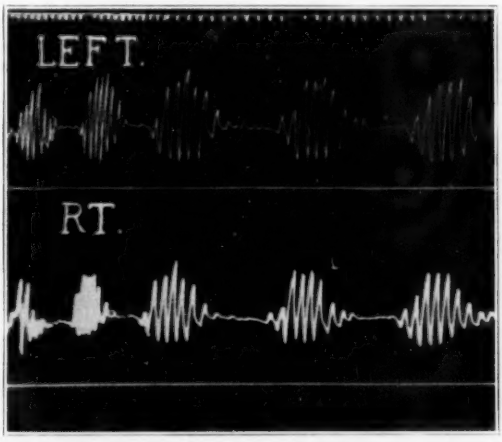

Fig. 1.—Bilateral pneumographic tracings of periodic breathing in a case of pseudobulbar palsy. (Dr. R. V. Grimmer provided these tracings and those in figure 3.)

inappropriate. In not a few cases the emotional exhibition, though elicited by trifling but appropriate impulses, is excessive and out of proportion to the impressions originating it. In others, a stimulus of a particular quality is followed by an emotional outburst of a contradictory sort. The visible emotion need not correspond to the patient's real feelings at the time.

In some instances the emotional response is invariable, whatever the stimulus. Some of the sufferers do nothing but laugh; others can

16. Wilson, S. A. K.: Pathological Laughing and Crying, J. Neurol. & Psychopath. **4**:299, 1924; Modern Problems in Neurology, New York, William Wood & Company, 1929, chap. 12.

only weep. A generalization suggests that patients having multiple sclerosis with pseudobulbar palsy manifest cheerfulness, whereas in arteriosclerotic patients sadness seems to predominate.

At the same time, the emotional display is a genuine show of feeling which no one can doubt. It differs from normal emotional reactions in its inevitability, frequency and uncontrollable character, in the occasionally contradictory relation of cause and effect and in the extreme facility with which it is induced; in expression and accompaniments it is identical. Photographs of 3 patients laughing and crying are presented (fig. 2). The first patient (figs. 2 *A* and 2 *B*) had periods of laughing and crying; the second (figs. 2 *C* and 2 *D*) only laughed. The third patient (figs. 2 *E* and 2 *F*) cried spontaneously or at the slightest verbal stimulus.

In laughter there is participation of the facial and respiratory musculatures as well as of other bodily mechanisms. The automatic rhythm of respiration is interrupted by prolonged inspirations followed by short and broken expirations. Coupled with these respiratory movements are laughter sounds of laryngeal origin and of varying character and pitch. If laughter is overwhelming, other muscles besides those of the face and respiratory apparatus are implicated; in fact, there may be much concomitant movement of the trunk and extremities.

Crying may utilize either the inspiratory or the expiratory phase of the cycle. There is a marked vasoconstrictor effect which explains the pallor, sunken features and sensations of cold and lassitude. Study of facial and respiratory movements is the basis for an analysis of the mechanism of response. However, some of the patients change rapidly from laughing to crying, and it is somewhat difficult on observation to be sure what emotion they are expressing. In figure 3 simultaneous spirographic and pneumographic tracings taken during one outburst of forced crying are presented. Inspiration is recorded as a downstroke in the spirograph which oscillates with movements of the air column. At the same time an upstroke occurs in the pneumograph, representing epigastric movement. Time is recorded in seconds. It will be noticed that crying began a little before the point *A*, halfway through a quiet expiration. Rapid, spasmodic, rhythmic but irregular contractions of the expiratory musculature followed for seventeen seconds. According to the spirograph, a few of the early contractions forced air past the closing glottis and caused audible sobbing to the point *A*; thereafter the glottis closed and weeping was silent. An apparent inherent tremulousness is present in the pneumograph tracing during quiet breathing and may represent persistent "undercurrent" sobbing respiration. These movements are too rapid to be transmitted aortic impulses.

The facial muscles have three distinct types of action: reflex (as respiratory muscles), emotional (as muscles of expression) and voluntary (as muscles subject to cerebral control). The ease with which the reflex and emotional control over the facial musculature creeps through or escapes from voluntary repression is frequently conspicuous in normal persons. The point at which this occurs retains a threshold value for

Fig. 2.—*A*, patient with hypertensive and syphilitic vascular disease, bilateral cerebral thromboses, double hemiparesis and pseudobulbar palsy. Note the atonic face, with predominant sadness. *B*, same patient, exhibiting pathologic laughing. *C*, another patient with hypertensive and syphilitic vascular disease, bilateral cerebral thromboses, double hemiparesis and pseudobulbar palsy, showing the tendency to a spastic facies with deepened nasolabial furrows and predominant cheerfulness. *D*, same patient, exhibiting forced laughing. *E*, patient with hypertensive vascular disease, multiple cerebral thromboses, double hemiparesis and pseudobulbar palsy, also manifesting a spastic facies but showing predominant sadness. *F*, same patient, showing forced crying.

each patient, balancing the strength and type of the underlying emotional or reflex stimulus against a labile volitional force that is subject to fluctuations of attention as well as to various physiologic and anatomic changes.

Nothnagel [17] postulated the existence of an emotional reflex pathway distinct from the corticobulbar fibers. He stated the opinion that the optic thalamus forms the origin of the efferent tract. No anatomic evidence for this theory has been found.

Brissaud [18] assumed that the integrity of the thalamus is essential for the appearance of spasmodic laughing and crying. He stated the belief that thalamic activity is ordinarily held in check by a frontothalamic tract running in the anterior limb of the internal capsule.

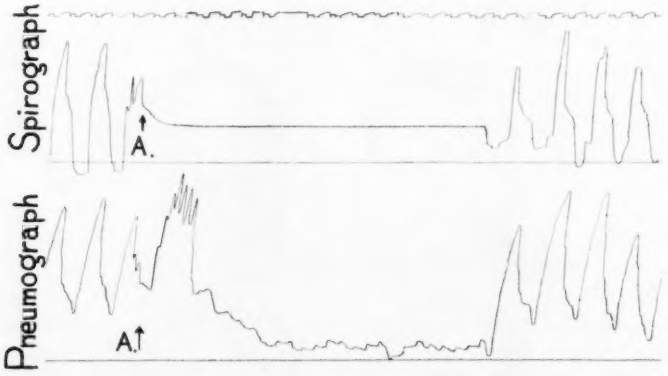

Fig. 3.—Simultaneous spirographic and pneumographic tracings made during one outburst of forced crying.

Wilson,[16] in 1929, based his theory of mimetic overreaction on the participation of both the facial and the respiratory mechanism. Bell [19] called the seventh nerve "the facial nerve of respiration," and paralysis of the lower part of the face was described by him as "paralysis of the respiratory functions of the facial." One may speak, therefore, of the faciorespiratory mechanism. The automatic activity of this mechanism is set aside voluntarily when one deliberately holds the breath or takes deep breaths and more or less voluntarily when one pants, coughs,

17. Nothnagel, H.: Topische Diagnostik der Gehirnkrankheiten, Berlin, A. Hirschwald, 1879.

18. Brissaud, E.: Leçons sur les maladies nerveuses, edited by H. Meige, Paris, G. Masson, 1895.

19. Bell, C.: The Nervous System of the Human Body, ed. 3, London, H. Renshaw, 1844.

yawns or sighs. Its activity is set aside involuntarily when one is convulsed with laughter or gives way to crying. One obtains, therefore, a glimpse of a triple control over faciorespiratory movements.

The paths of voluntary impulses to facial and respiratory muscles are undoubtedly the corticobulbar and corticospinal tracts. In particular, the fibers from the operculum and the lower end of the precentral gyrus, running in the genu of the internal capsule, convey the impulses to the bulbar nuclei. Lloyd's case, to be described later, bears out this concept. Injury of the corticobulbar fibers impairs volitional control over the muscles concerned in emotion, with the result that the involuntary action of the same muscles tends to be overactive. The more severe the volitional faciorespiratory paralysis, the more exaggerated is the loss of emotional control. Emotional activity is often distinctly increased on the paretic side in patients with hemiplegia.

There is little evidence for the exact localization of the faciorespiratory involuntary control. Brown [20] found a small area in the mesencephalon of the chimpanzee, between the internal border of the red nucleus and the midline, which on stimulation gave responses similar to laughing. Likewise, the experimental work of Bard [21] on sham rage in cats, as well as that of Lilienthal and Otenasek [22] on polypnea in decorticate animals, demonstrates the release of diencephalic mechanisms controlling the emotional and reflex responses of the faciorespiratory muscles.

5. *Jaw Jerk.*—An unusually active jaw jerk is an important sign of bilateral injury to the corticobulbar fibers. This reflex, like all other deep reflexes, becomes exaggerated when released from cerebral control.

6. *Allied Phenomena.*—Mental deterioration of varying degrees and types is frequently seen, especially in old arteriosclerotic persons with progressive diffuse cortical softening. Certain patients have cataleptic periods, during which they remain perfectly quiet with the eyes fixed. The sucking reflex is often demonstrable. Other patients may exhibit tonic perseveration, forced grasping and groping, recently shown to depend primarily on lesions of the premotor cortex. Figure 4 shows a patient with pseudobulbar palsy in whom forced grasping as well as the sucking reflex was demonstrable. Some patients have an unusually large appetite and eat ravenously.

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20. Brown, T. G.: Note on the Physiology of the Basal Ganglia and Mid-Brain of the Anthropoid Ape, Especially in Reference to the Act of Laughter, J. Physiol. **49**:195, 1915.

21. Bard, P.: On Emotional Expression After Decortication with Some Remarks on Certain Theoretical Views, Physiol. Rev. **41**:309, 1934.

22. Lilienthal, J. D., and Otenasek, F. J.: Decorticate Polyneic Panting in the Cat, Bull. Johns Hopkins Hosp. **61**:101, 1937.

VARIATIONS IN THE SYNDROME AS RELATED TO THE LOCATION OF THE CEREBRAL INJURY

The three chief symptoms of the syndrome, difficulties of speech, difficulties of swallowing and emotional instability, may be developed in varying degrees in individual patients and at different stages of the

Fig. 4.—*A*, patient with multiple cerebral thromboses, right hemiplegia, left hemiparesis and pseudobulbar palsy, demonstrating forced grasping. *B* and *C*, same patient, showing the sucking reflex.

disease. Other associated abnormalities are dependent on injury of other pathways in the brain. These modify the primary abnormalities and often serve to localize more accurately the disease process.

Symmetric areas of softening of the motor cortex in the lower portion of the prefrontal area and the operculum destroy the cerebral control

of the bulbar muscles. This type of lesion may result from embolism or thrombus formation. In cases of cortical softening the corticobulbar fibers may be damaged selectively, leaving the corticospinal pathway practically or wholly uninjured.

Alajouanine and Thurel [23] described the clinical picture of pseudobulbar palsy produced by bilateral lesions of the cerebral motor cortex. The paralysis is limited to the masticatory muscles and those of the face, larynx, pharynx and tongue; there are weakness and restriction of ocular movements. Involvement of the extremities is slight and transient. Atonia is usually present, which explains why laughing and crying lack their usual spasmodic character.

The lesions responsible for pseudobulbar palsy occur perhaps most frequently in the internal capsules. A case reported by Lloyd [24] was unique in that there were bilateral vascular leisons confined to the genu of each internal capsule and adjacent lenticular nucleus, creating typical pseudobulbar palsy without manifest involvement of the corticospinal tracts. Often there are diffuse small areas of encephalomalacia dependent on arteriosclerosis. These softenings are found also in the basal ganglions and may give rise at the same time to the parkinsonian syndrome. Thus diffuse rigidity may form a background for the pseudobulbar palsy. The face may show the immobility associated with the parkinsonian syndrome as well as the characteristic features of pseudobulbar palsy. It must be realized, of course, that parkinsonian rigidity in itself gives rise to difficulties of speaking and swallowing. The tremor may be evident in speech.

Pontile lesions may be responsible for the syndrome. Injury of cerebellar pathways as well as of the corticobulbar tracts may be found. The incoordination of speech and breathing is suggestive of that associated with isolated damage to the cerebellum.

The sharp differentiation of these various secondary manifestations from the primary symptoms of pseudobulbar palsy is seldom made. We maintain that the characteristic findings of difficulty in speech and swallowing combined with emotional instability are always dependent on bilateral injury of the corticobulbar fibers.

DISEASE PROCESSES WHICH OFTEN PRODUCE THE SYNDROME OF PSEUDOBULBAR PALSY

In the majority of cases pseudobulbar palsy results from cerebral vascular lesions. Arteriosclerosis or syphilitic vascular disease with thrombotic softenings may be demonstrated in the brain in many cases.

23. Alajouanine, T., and Thurel, R.: La diplégie faciale cérébrale, forme corticale de la paralysie pseudobulbaire, Rev. neurol. **2**:441, 1933.

24. Lloyd, J. H.: Pseudobulbar Palsy, Internat. Clin. **4**:210, 1908.

Thrombosis of the median group of fine pontile and vertebral arteries tends to produce the syndrome. In certain cases of cerebral vascular disease, especially the more acutely developing conditions, the typical features of pseudobulbar palsy may be strongly marked for a time and may then regress. There is a small group of cases in which the syndrome is caused by tumors or by infectious processes.

Patients with multiple sclerosis may have pseudobulbar palsy, particularly in the later stages of the disease; more often only a portion of the syndrome is present. Emotional instability is extremely common. Disturbances of speech and sometimes difficulties in swallowing occur. Bilateral involvement of the corticoefferent fibers is most commonly due to plaques in the pons, so that difficulties of speech and swallowing in these cases may be modified by the incoordination commonly associated with injury of the cerebellum.

Certain familial diseases may produce the syndrome of pseudobulbar palsy. In Friedreich's ataxia there is involvement of the corticobulbar and corticospinal tracts. Forced laughing and crying are strongly developed. Signs of cerebellar disease are combined with the syndrome. Syringobulbia may produce damage to the brain stem and give rise to emotional instability and to difficulties in speaking and swallowing.

True bulbar and pseudobulbar palsy occur together in amyotrophic lateral sclerosis. In this disease there is degeneration of the lower motor neurons in the nuclei of the cranial nerves and anterior columns of the spinal cord as well as degeneration of the Betz cells. In certain cases the lower motor neurons degenerate first and more severely; in others the corticobulbar and corticospinal pathways bear the brunt of the damage. In the latter instances typical symptoms of pseudobulbar palsy are observed. Often, with the whole syndrome present, it is possible also to demonstrate fibrillations and atrophy in the facial and masticatory muscles and in the tongue.

DIFFERENTIAL DIAGNOSIS

Conditions in which weakness of the muscles or damage to the lower motor neurons of the cranial nerves occur alone must be differentiated from pseudobulbar palsy. In such conditions emotional instability is absent, but there may be profound difficulties in speech and deglutition. This is true of myasthenia gravis, progressive muscular atrophy or any condition involving the medullary motor components. Pseudobulbar palsy is differentiated by its frequent association with hemiplegia or quadriplegia, the absence of wasting, fibrillation or reaction of degeneration in the muscles supplied by the cranial motor nuclei, retention and frequent exaggeration of the jaw jerk and the characteristic phenomena of emotional release. The syndrome may occur with true bulbar palsy,

in which case interpretation is more difficult. Likewise, a condition of pseudobulbar palsy may be obscured by the shock immediately following a cerebral vascular accident or by increased intracranial pressure. In a recent paper, Karnosh and Connor [25] stated significantly: "Pathologic grimacing is a transitory phenomenon, frequently dependent on the locale of the lesion and clearing as the hemiplegia improves. It may therefore escape detection and, in many cases of central nervous system syphilis, be regarded as a manifestation of the emotional derangement of dementia paralytica."

25. Karnosh, L. J., and Connor, W. H.: Syphilitic Pseudobulbar Palsy with Compulsive Weeping, Am. J. Syph., Gonor. & Ven. Dis. **20**:115, 1936.

PURPURA HAEMORRHAGICA DUE TO INGESTION OF SEDORMID (ALLYLISOPROPYL-ACETYLCARBAMIDE)

EXPERIMENTAL OBSERVATIONS AND REPORT OF A CASE

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In 1933, Dennig [1] reported 3 cases of purpura haemorrhagica due to oral administration of iodifix, a preparation containing iodine. One of the patients, a woman aged 64, after recovery from iodine purpura had two distinct relapses, each following the use of 1 tablet of sedormid (allylisopropylacetylcarbamide), a drug that she had not used previously. From 1933 to October 1938 reports of instances of purpura haemorrhagica following the use of sedormid [2] appeared in rapidly increasing

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Supported by a grant from the Christine Breon Fund.

From the Department of Medicine, University of California Medical School.

1. Dennig, H.: Thrombopenische Purpura nach Jodeinnahme, München. med. Wchnschr. **80**:562 (April 14) 1933.

2. (*a*) Loewy, F. E.: Thrombopenic Haemorrhagic Purpura Due to Idiosyncrasy Towards the Hypnotic Sedormid: Allergotoxic Effect, Lancet **1**:845 (April 21) 1934. (*b*) Graubner, W., cited by Hadorn.[2i] (*c*) Stern, R.: Psychose bei Purpura cerebri infolge Sedormidüberempfindlichkeit, Wien. klin. Wchnschr. **49**:1288 (Oct. 16) 1936. (*d*) Falta, W.: Fall von Sedormidpurpura, ibid. **49**: 798 (July 19) 1936. (*e*) König, F., in discussion on Falta.[2d] (*f*) Decastello, A., in discussion on Falta.[2d] (*g*) Glasz, E., in discussion on Falta.[2d] (*h*) Pollacsek, K. F., in discussion on Falta.[2d] (*i*) Hadorn, W.: Purpura thrombopenica durch Sedormid, Schweiz. med. Wchnschr. **17**:1273 (Dec. 12) 1936. (*j*) Vogl, A.: Thrombopenische Purpura nach Sedormidgebrauch, Wien. klin. Wchnschr. **48**: 908 (July 5) 1935. (*k*) von Lauda, E., in discussion on Vogl, A.: Die Pathogenese der akuten thrombopenischen Purpura, Wien. med. Wchnschr. **86**:1118 (Oct. 3) 1936. (*l*) Boas, E. P., and Erf, L. A.: Thrombocytopenic Purpura Following Medication with Sedormid (Ureide Preparation) and with Phenobarbital, New York State J. Med. **36**:491 (April 1) 1936. (*m*) Peck, S. M.; Rosenthal, N., and Erf, L. A.: Value of Prognostic Venom Reaction in Thrombocytopenic Purpura, J. A. M. A. **106**:1783 (May 23) 1936. (*n*) Mettier, S. R., and Stone, R. S.: Effect of Roentgen Ray Irradiation on Platelet Production in Patients with Essential Thrombocytopenic Purpura Haemorrhagica, Am. J. M. Sc. **191**: 794 (June) 1936. (*o*) van Andel, P., and Groen, J.: Thrombopenic Purpura (Werlhof's Disease) After Use of Sedormid, Nederl. tijdschr. v. geneesk. **81**:

numbers, as evidenced by our having found, in the literature covering this period of approximately five years, reports of 41 cases. Including our reported case, the total number of cases at the time of writing (November 1938) is 42. We have prepared a table (table 1) setting forth the names of the authors and their reports of cases during the period mentioned. Pertinent data in connection with these published cases have been tabulated for comparison and study. Some of the details we are interested in are lacking, but we believe all of the 41 cases are well authenticated instances of thrombopenic purpura due to ingestion of sedormid.

The table shows 24 women and 12 men, as indicated by the reports in which the sex was stated. Of the women, 20 were over 35 years of age; 14 were over 48, and in 2 instances the age was not stated. Of the men, 1 was 32, 2 were 43, and the remaining 9 were over 50. In 4 cases neither sex nor age was stated. The cases indicate an increased susceptibility to the purpuric manifestations of sedormid among the older age groups in both sexes. In the instances in which platelet counts were made at the time of the purpuric manifestations, the number per cubic millimeter was usually below 80,000. There were 2 exceptions to this. In case 31 (reported by Hoffman, Kahn and Fitzgibbon [2r]) the platelet count was 152,000 on the second day after taking ½ tablet of sedormid. However, the attack was reproduced by the ingestion of 1 sedormid tablet, and the number of platelets recorded the morning following the taking of the sedormid was 59,000 per cubic millimeter. In case 38 (reported by Hill [2v]) the platelet count was 180,000 on the day following ingestion of the last sedormid tablet. As indicated in table 1, the white cell count during the attack varied from 4,900 to 5,600 per cubic millimeter in 5 cases and from 6,800 to 10,400 in 7 cases and was 20,000 in 1 case. The hemoglobin determinations and the red blood cell counts are not recorded in table 1, since no information is available concerning the presence of anemia prior to the attack. There are too few observa-

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3348 (July 10) 1937. (*p*) Kramer, P. H.: Purpura Hemorrhagica After Use of Sedormid, ibid. **81**:3345 (July 10) 1937. (*q*) Lieberherr, W.: Zur Kenntnis der Purpura thrombocytopenica beim Bebrauch von Sedormid, Med. Klin. **33**:475 (April 2) 1937. (*r*) Hoffman, A. M.; Kahn, J., and Fitzgibbon, J. P.: Thrombocytopenic Purpura Following Allyl-Isopropyl-Acetyl-Carbamide (Sedormid), J. A. M. A. **110**:725 (March 5) 1938. (*s*) Moody, A. M.: Thrombocytopenic Purpura Following Use of Allyl-Isopropyl-Acetyl-Carbamide (Sedormid), ibid. **110**:726 (March 5) 1938. (*t*) Torrens, J.: Purpura Following Sedormid, Lancet **1**:749 (March 26) 1938. (*u*) Joekes, T.: Purpura Haemorrhagica (Werlhof's) After Taking Sedormid, ibid. **2**:305 (Aug. 6) 1938. (*v*) Hill, D. B.: Thrombopenic Purpura Following Allyl-Isopropyl-Acetyl-Carbamide (Sedormid), J. A. M. A. **111**:1459 (Oct. 15) 1938. (*w*) Naegeli, O.: Differentialdiagnose in der inneren Medizin, ed. 2, Leipzig, Georg Thieme, 1936; cited by Joekes.[2u] Dennig.[1]

tions recorded on the marrow of the sternum to permit any conclusions. Recovery is apparently rapid as soon as the drug is discontinued. In the majority of the cases from three to eight or ten days has seen complete clearing of the purpura, with cessation of bleeding. Treatment, including such measures as roentgen therapy, administration of vitamin C, blood transfusion, giving of calcium or intramuscular administration of liver extract, apparently has not shortened the interval of recovery. The amount of sedormid necessary to cause sensitization varies greatly. After sensitization the amount of the drug necessary to reproduce the purpuric and hemorrhagic phenomena is small, usually 1 or 2 tablets.

REPORT OF CASE

History.—M. G., a white woman aged 26, single, was admitted to the University of California Hospital on June 19, 1937, complaining of small dark spots and larger "black and blue" areas, scattered on and beneath the skin of her entire body. Her symptoms began about May 29 (three weeks before admission to the hospital), at which time she noted small reddish spots, "like grains of red pepper," scattered over her lower extremities. Successive crops of spots of this type appeared until all the skin of the body was involved. In addition, large "black and blue" areas, a few 6 or 8 cm. in diameter, appeared over the lower part of the abdomen and the lower extremities. A few of these ecchymotic areas were very tender on pressure. At the time of entry there was slight bleeding from the gums. The last four menstrual periods had occurred one week earlier than usual, and the flow had been more profuse.

She had had an operation at the age of 19 for removal of the appendix and for suspension of the uterus. At the age of 15 she began to suffer from hay fever, which recurred every spring when she was in the San Joaquin Valley and San Francisco Bay area. She began having bronchial asthma at the age of 22. For the first two years it was experienced only in the spring and accompanied the hay fever. During the past year, however, it was present more or less continuously, having failed to clear up at the end of the hay fever period of spring. The asthmatic attacks were especially troublesome at night, when the wheezing and coughing were severe. Skin tests at the age of 15 showed positive reactions to pollen, but no pollen hyposensitization was ever attempted. In addition to the hay fever, bronchial asthma and purpura, the only allergic history obtainable was that of the invariable production of an asthmatic attack by the drinking of beer. In the patient's opinion, her daily diet has been somewhat restricted. It has included orange or tomato juice, graham crackers, coffee, soups, canned beans, milk, sandwiches, salads, vegetables, meats and desserts. For the past year the only medication aside from sedormid had been pills of ferrous carbonate U. S. P. The history of sedormid medication went back to a period about six months before admission, when the patient began to take 1 to 2 or 3 tablets a week for sleep, depending on the frequency and severity of her asthmatic attacks. During her midterm college examinations (April 1937) she took about 4 tablets in one week. At this time she noted a slight scattering of petechiae during her menses. Two months later, she again took 4 or 5 tablets during one week (May 21 to 29), after which the attack occurred for which she was admitted to the hospital. However, she continued to take 1 tablet nightly up to the day of admission.

In the hospital she was given a high vitamin, unrestricted diet, 0.6 Gm. of reduced iron four times daily and 4 Gm. of calcium gluconate three times a day. During the first five days in the hospital the patient was given 0.05 Gm. of amytal each night. During the first nine days in the hospital she received 0.025 Gm. of ephedrine sulfate for eleven doses and two injections of a 1:1,000 dilution of epinephrine, 0.5 and 0.25 cc., respectively.

Dermal and intradermal tests showed many positive reactions to spring, summer and fall pollens. No positive reactions were obtained to house dust, animal danders, miscellaneous inhalants, eggs, milk, the common cereals, meats, vegetables or fruits.

Physical Examination.—Petechiae were found scattered over the trunk and extremities. A small hematoma was observed beneath the right lower eyelid, and large ecchymotic areas were present over both arms and the region of the iliac crests. On both thighs were large ecchymotic areas from 8 to 10 cm. in diameter, and over the lower extremities similar areas from 6 to 8 cm. in diameter (fig. 1). Some areas over the lower extremities were very tender on moderate pressure.

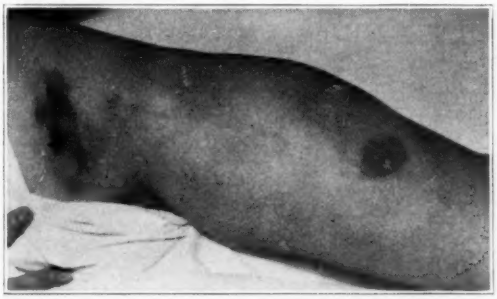

Fig. 1.—Ecchymoses on the left thigh and lower part of the abdomen.

The blood pressure was 110 systolic and 65 diastolic. The heart was not enlarged, and there were no murmurs. Neither spleen nor liver was felt. An examination of the pelvis revealed nothing abnormal. The lungs were normal.

Laboratory Data.—On June 21 the ascorbic acid content of the plasma was 0.78 mg. per hundred cubic centimeters. The results of Dalldorf capillary fragility tests on the upper part of the left arm showed showers of petechiae with —20 cm. pressure, 30 to 40 petechiae, with —15 cm. pressure and 6 to 8 petechiae with —10 cm. pressure.

The Kolmer modification of the Wassermann and Kahn tests of the blood gave negative reactions. On June 20 the urine showed no red blood cells. On June 24 the stool gave a negative reaction to the test for occult blood. On June 20 the blood clotting time (Lee and White) was three and one-half minutes, with a bleeding time (Duke) of six minutes. The platelet count on June 23 was 130,000 per cubic millimeter.

Experimental Procedures.—On June 26 0.5 Gm. of sedormid was dissolved in 5 cc. of distilled water. A piece of blotting paper saturated with this solution was placed on the skin with adhesive tape. After forty-two hours no reaction of any kind had taken place locally. During this period there was no significant alteration

TABLE 1.—*Cases of Purpura Haemorrhagica Due to Sedormid in the Literature from 1933 to 1938*

Author	Case	Sex	Age	No. of Platelets A. Height of Attack R. After Recovery	Effects on Blood Cells Other Than Platelets	Previous Allergy or Purpura	Approximate Time for Recovery	Treatment	Amount of Sedormid Taken Before Purpura Appeared	Attacks Reproduced Experimentally or Accidentally
Dennig [1] (1933)	1	M	64	A. 48,000, 12/14/33 15,000, 12/15/33 R. 50,000, 12/23/33	.....	Sensitive to iodine	.....	.....	Two relapses each time after use of 1 tablet	Yes
Loewy [2a] (1934)	2	M	61	A. 22,000, 10/ 5/31 R. 360,000, 10/16/31	A. White cells 9,600; anemia, myelocytes present R. 9,600	Irritable colon, pruritus	6 days	Transfusion	1-2 tablets frequently over period of 3 years	Yes
	3	F	60	A. 28,000 R. Normal	A. White cells 6,800, eosinophils 9.4%, slight anemia, neutropenia	Nervous indigestion	7 days	None	1-2 tablets per night for 5-6 weeks	No
	4	F	51	A. 36,000, 2 days after drug	.....	.....	No further spots after stopping drug	Transfusion	½-1 tablet repeatedly for 1 year	No
Graubner [2b] (1934)	5	M	59	Platelets diminished	.....	.....	.....	.....	3 tablets daily for 8 months	Yes
Stern [2c] (1936)	6	M	63	.....	.....	None mentioned	8-10 days	None	1931: several tablets, no symptoms; 1934: 1 tablet, purpura; June 1935: 2 tablets, chills, fever, purpura, psychosis	No
Falta [2d] (1936)	7	F	57	A. 20,400, 4/25/36 R. 417,500, 5/ 4/36	White cells 5,400	None mentioned	Immediately after cessation of drug	None	2½ tablets daily for several weeks without symptoms; stopped drug for 2 weeks; on taking it again had attack purpura haemorrhagica	Yes
König [2e] (1936)	8	F	68	.....	.....	Intestinal hemorrhage	.....	None	.....	No
Decastello [2f] (1936)	9	M	55	A. 27,000, 3/28/36 125,000, 4/ 3/36	.....	.....	.....	Ascorbic acid (cantan)	21 tablets in 14 days	No
Glasz [2g] (1936)	10	M	68	Purpura occurred on initial use of drug		.....	.....	.....	1 tablet	No
Pollacsek [2h] (1936)	11	F	Young girl	No platelet count made	.....	.....	Severe attack with rapid recovery	None	Unknown number of tablets, with suicidal intent	No

Hadorn [21] (1936)	12	F	47	A. 26,400, 5/13/36 R. 206,400, 5/26/36	A. White cells 5,600, slight leukopenia, aspiration of sternal marrow showed very active regeneration of platelets R. White cells 6,800	None	8-9 days	None	1-2 tablets per week for 11 weeks	...
	13	M	65	A. 10,500, 8/15/36 R. 105,500, 8/19/36	White cells 5,600, 8/19/36	None	6 days	None	1 tablet August 11 and 1 on Augst 13	No
	14	F	26	A. Very few platelets seen on smear 1/22/36 R. Platelets appear normal on smear 4 days after taking 1 tablet, 1/26/36	A. White cells 5,500	None	3 days	Sangostop (a vitamin C preparation) by mouth and injection, without result; drug stopped; immediate improvement	1 tablet each evening for several months	No
A. Vogl [21] (1935)	15	M	68	A. Complete disappearance of platelets	.....	.....	3 days	2 roentgen ray exposures	Took drug without symptoms for 1½ years, then 2 tablets in 5 months' interval; each produced an attack of purpura	No
	16	F	70	A. 10 hours after sedormid complete disappearance of platelets R. 325,000	.....	.....	3 days	2 roentgen ray treatments	Took sedormid 1 month without symptoms; report states small dose caused attack	No
Lauda [2k] (1936)	17	Details of case lacking				.....	About 3 days	.....	.....	No
Boas and Erf [21] (1936)	18	F	47	A. 70,000 R. 190,000	Biopsy of sternal marrow showed normal marrow 10½ days after onset of acute attack, slight anemia, monocytes 7-8% A. White cells 10,400	Fats caused discomfort in gastrointestinal tract	6 days	None	1 month previously, attack after 1 tablet; 1 tablet 2 successive nights before present attack	Yes
Peck and his associates [2m] (1936)	19	F	63	A. 20,000 R. 6 days after attack 260,000	White cells 20,000	.....	Immediate when drug was stopped	None	Sedormid for 1 month previous to admission to hospital, amount not stated	No
	20	F	48	.....	.....	.....	Recovered with removal of drug	None	.....	Yes
	21	F	?	No details		.....	.....	None	.....	No

TABLE 1.—*Cases of Purpura Haemorrhagica Due to Sedormid in the Literature from 1933 to 1938—Continued*

Author	Case	Sex	Age	No. of Platelets A. Height of Attack R. After Recovery	Effects on Blood Cells Other Than Platelets	Previous Allergy or Purpura	Approximate Time for Recovery	Treatment	Amount of Sedormid Taken Before Purpura Appeared	Attacks Reproduced Experimentally or Accidentally
	22	M	32	A. 12/16/35, 2,000 12/18/35, 20,000 12/19/35, 40,000 12/20/35, 70,000 12/23/35, 260,000	.....	.....	.....	None	.....	No
Mettler and Stone [2n] (1936)	23	F	67	A. 40,000 R. After 6 days 300,000 R. After 12 days 468,000	.....	.....	6 days	Roentgen therapy	.....	Yes
van Andel and Groen [2o] (1937)	24	F	60	A. ..... R. 242,000	White cells 6,300	None	12 days	None	10 tablets during 9 day interval	Yes
	25	M	43	A. 9,000 R. 146,000	White cells 10,900	Bleeding from gums	3 weeks	None	5 tablets during 9 day interval	No
	26	F	32	A. Marked reduction in platelets	.....	.....	.....	Calcium gluconate	Drug taken at intervals for 5 months; then attack after 1 tablet	No
Kramer [2p] (1937)	27	M	54	A. Occasional platelet	.....	.....	2 weeks	Calcium by mouth, redoxon (vitamin C, tablet form), fruit juices	2 tablets each night for 2-3 years, last dose (2 tablets) night before being seen by author	14 days after recovery took 1 tablet on 2 successive evenings with return of purpura
Lieberherr [2q] (1937)	28	F	65	1. A. 23,000, 2/22 R. 310,000, 3/9	A. White cells 4,900; polymorphonuclears 69.6%; slight anemia and leukopenia; sternal puncture, megakaryocytes 1%	None	17 days	Liver extract, 5 cc. daily for 6 days; redoxon (vitamin C) 100 mg. intravenously, 12 daily doses, 4 doses evening second day	1 tablet, initial dose	Yes
				2. A. 5,700, 9/2 R. 320,000, 9/23	Anisocytosis of platelets, some size of a red cell					
	29	F	45	A. 37,000, 3/12/35 9,000, 3/18/35 R. 200,000, 4/9/35 405,000, 5/27/35	White cells 7,500, 3/13/35; monocytes 9%	.....	27 days	Redoxon, 100 mg. intravenously, 4 doses; liver extract, 4 injections	40 tablets taken over an interval of 6-7 months	No

Hoffman and his associates [2r] (1938)	30	F	37	A. 55,000 R. Stated to have been normal	White cells 5,200, eosinophils 0.5%	No family or personal history of allergy	5 days	None	1 tablet 4 or 5 times over period of several months before attack; 1 tablet at night before each of 3 attacks	No
	31	F	37	A. 152,000 R.	White cells 9,350; neutrophils show moderate toxic granulation, some shift to left	.....	Purpura fading in 3 days	None	About 30 tablets past 3 years, none for several weeks, then ½ tablet night before attack	Yes
	32	M	56	A. 40,000 R. 239,000	White cells 9,100, 5/10/37	Typhoid vaccine for arthritis	12 days	None	2 tablets 2 days apart	Yes
Moody [2s] (1938)	33	F	60	A. 16,384, 2/12/37 R. 378,000, 3/1/37	A. White cells 7,000; polymorphonuclears 70%; anemia	.....	18 days	Moccasin snake venom	6 tablets over period of 1 year	No
	34	F	45	No counts made	.....	.....	5 days	.....	20 tablets over 2 weeks' time	No
Torrens [2t] (1938)	35	..	Middle age	A. 80 (?) per cu. mm.	Anemia, red cells 50% of normal	.....	Recovery rapid when drug was stopped	None except high calcium diet	1 tablet every night for 1 to 3 months	No
	36	..	Middle age	.....	.....	.....	Recovery rapid when drug was stopped	High calcium diet	1 tablet every night for 1 to 3 weeks	No
Joekes [2u] (1938)	37	M	43	A. 13,600 A. 800 per cu. mm. 8 days after first count	.....	.....	10 days	None	Sedormid regularly over long periods	No
Hill [2v] (1938)	38	F	70	R. 334,000 A. 180,000	.....	.....	10 days	.....	In June 1936 some tablets taken, November 1936 1 each night for about 1 week before attack	No
	39	F	48	No details given		.....	Prompt recovery after stopping drug	.....	For several weeks, one tablet at night	No
Naegell [2w] (1936)	2 cases									

in the platelet counts or any diminution in the total number of white cells or granulocytes, as reported by Squier and Madison [3] in their studies on sensitivity to aminopyrine.

On June 27 the blood count showed 11.78 Gm. (86 per cent) of hemoglobin, 4,560,000 red blood cells and 9,600 white blood cells. The differential count showed 71 per cent neutrophils, 15 per cent lymphocytes, 9 per cent eosinophils, 1 per cent basophils, 4 per cent monocytes and 0.4 per cent reticulocytes.

The pressure cuff applied to the right arm at a pressure of 76 mm. of mercury for five minutes caused no petechiae to appear.

Fig. 2.—Results of the Dalldorf capillary fragility tests during the patient's first stay in the hospital. The more distinct hemorrhagic areas represent — 20 cm. pressure.

On June 28 at 9:10 a. m. ½ tablet of sedormid was administered. At 12 o'clock noon, the platelet count was 310,000 per cubic millimeter, but by 5:30 p. m. the count had dropped to 100,000.

On June 29 the platelet count was 110,000 per cubic millimeter. The patient was given 2 sedormid tablets at 10 a. m. The platelet count at 11:15 a. m. was 120,000,

3. Squier, T. L., and Madison, F. W.: Primary Granulocytopenia Due to Hypersensitivity to Amidopyrine, J. Allergy **6**:9 (Nov.) 1934.

but by 5 p. m. it had fallen to 40,000. The pressure test on June 29 at 10 a. m., with 84 mm. of mercury pressure for five minutes, showed many petechiae below the cuff. At 5 p. m. of the same day application of the Dalldorf instrument to the upper part of the right arm caused showers of petechiae with —20 cm. pressure, scattered showers of petechiae with —15 cm. pressure, 8 to 9 petechiae with —10 cm. pressure. On the same day petechiae appeared over the posterior axillary folds and on the buttocks.

From June 29 until July 5 eight more observations were made with the Dalldorf instrument, using each arm alternately. The readings did not vary significantly from the previous ones until July 4 and 5, on which days the readings at —15 and —10 cm. pressure showed a somewhat lessened number of petechiae to the field, probably indicating the beginning of a lessened capillary fragility

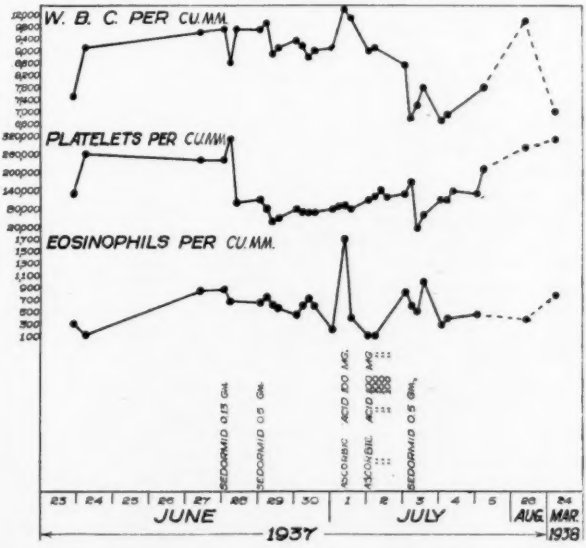

Fig. 3.—Correlation of platelet level and white blood cell and eosinophil counts.

on July 4. This test is undoubtedly a fairly delicate quantitative test of increased capillary fragility and has value in a situation such as this, in which we were interested in determining the time required for the capillaries to recover resistance under therapy with vitamin C (ascorbic acid) (fig. 2).

On June 30 the platelet counts varied from 70,000 to 90,000. Petechiae appeared over the chest, arms and neck.

On July 1 the platelets varied between 80,000 and 90,000. At 8 a. m. 100 mg. of ascorbic acid was administered intravenously and the dose was repeated four times during the day, at intervals of four hours. At 9 p. m. there was an epistaxis of 4 to 5 cc. On July 2 the platelets rose to 140,000. There were two slight epistaxes during the day. The ascorbic acid content of the plasma was 1.09 mg. per hundred cubic centimeters.

On July 6 the patient was discharged from the hospital, at her request, but she promised to return later for further studies. The platelet count was 210,000 on July 6, and the purpuric lesions of the skin had nearly disappeared.

Our diagnosis was purpura haemorrhagica due to the ingestion of sedormid. The chart giving results of detailed daily studies of the blood has not been included, as the values for the red cells and hemoglobin remained fairly constant, showing a slight increase, undoubtedly due to iron therapy while in the hospital. The number of red blood cells ranged from 4,550,000 on June 23 (on admission) to 5,060,000 on July 5 (at discharge), and the hemoglobin, from 11.78 Gm. (86 per cent) to 12.88 Gm. (94 per cent). The red cell counts were made with certified blood counting pipets (United States Bureau of Standards), and the hemoglobin estimations were made by the acid hematin method (Sahli hemoglobinometer). The Rees and Ecker method was used for the platelet counts. Figure 3 shows the correlation of platelet, white cells and eosinophil counts. This graph does not show the type of hematologic response described by Squier and Madison [4] as characteristic of thrombopenic purpura due to food allergy. In their reported cases, the ingestion of foods to which the patients were allergic caused an immediate sharp rise in eosinophils accompanied by a drop in the platelet and white cell counts. In our blood studies on this patient, no evidence of leukopenia or granulocytopenia, described as occurring after ingestion of aminopyrine, was noted in the daily white blood cell counts.

On Aug. 28, 1937, the patient reported for a blood count, which showed: 5,100,000 red blood cells, 12.33 Gm. (90 per cent) of hemoglobin, 10,300 white blood cells, 49 neutrophils, 3 eosinophlis, 1 basophil, 39 lymphocytes and 7 monocytes. The platelets numbered 280,000.

She reported again on March 24, 1938, at which time the blood showed 4,010,000 red blood cells, 11.5 Gm. (84 per cent) of hemoglobin, 7,900 white blood cells, 45 neutrophils, 10 eosinophils, 1 basophil, 35 lymphocytes and 9 monocytes. The platelets numbered 330,000.

Approximately one year after her first admission to the hospital, on July 7, 1938, the patient returned for further experimental study.

An outline of our plans for further investigation included (1) determination of the degree of the patient's sensitivity to sedormid, (2) observation of the rate of recovery from thrombocytopenic purpura induced by ingestion of sedormid after cessation of use of the drug and without specific administration of vitamin C, (3) aspiration and study of the marrow of the sternum before and during her experimentally induced attack of purpura and (4) tests of capillary fragility (Dalldorf method), to observe whether or not capillaries require a longer period for recovery of tone after an experimental attack of purpura when no vitamin C is administered (except that included in the regular hospital diet).

During the second experiment, no orange juice or lemon juice was supplied with the patient's hospital diet, but other fruit juices and vegetables were part of her regular daily meals.

Table 2 shows the amount of sedormid administered. During the period between 8 a. m. on July 7 and 7: 30 p. m. on July 14, 1938, 11½ tablets, or 28.75 Gm., of sedormid were given.

Capillary fragility tests (Dalldorf) before sedormid was administered on July 7 showed 20 petechiae with —20 cm. pressure and 6 to 10 petechiae

4. Squier, T. L., and Madison, F. W.: The Hematologic Response in Food Allergy Eosinophilia in the Leucopenic Index, J. Allergy **8**:250 (March) 1937; Thrombocytopenic Purpura Due to Food Allergy, ibid. **8**:143 (Jan.) 1937.

with —15 and —10 cm. pressure. Five and one-half hours after ½ tablet of sedormid was given (4 p. m., July 7), there was a slight increase in capillary fragility. By July 13 the increase was pronounced (fig. 4). By July 19 capillary fragility tests showed a relatively normal state. These tests corresponded rather closely to the degree of capillary fragility present during her attacks in 1937 (experimental and initial). The petechiae in the area where the Dalldorf instrument was applied were larger and more distinct during this second attack (fig. 4), when no specific vitamin C was administered. It will be noted in table 2 that, after the administration of the first ½ tablet of sedormid on

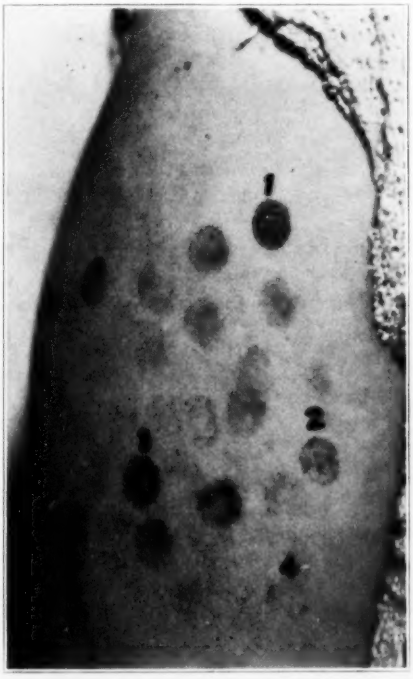

Fig. 4.—Results of the Dalldorf capillary fragility tests during the patient's second stay in the hospital. 1, with—20 cm. pressure; 2, with —15 cm. pressure; 3, with —10 cm. pressure, and 4, with —5 cm. pressure.

July 7, the number of platelets decreased gradually to 80,000 per cubic millimeter on July 13, when petechiae began to appear over the chest, neck and arms. By July 15 the entire body was covered with small purpuric spots, and on July 16 there appeared ecchymotic areas about 3 to 4 cm. in diameter over the anterior aspect of the upper part of the right thigh, the right shoulder and the front and back of the chest. The morphologic character of the platelets, as noted on the blood films, was not remarkable, but with reduction of platelets the films showed many small, dark, ragged disks. When the platelet count fell to 80,000 per cubic

TABLE 2.—*Record of Experimental Attack of Purpura Haemorrhagica Induced During Second Stay in Hospital* *

Patient—M. G.

Date, 1938	Dose of Sedormid	Time	Red Blood Cells, Millions	Hemoglobin %	Hemoglobin Gm.	Platelets	White Blood Cells	Polymorphonuclears: Neutrophils: Filamented	Polymorphonuclears: Neutrophils: Nonfilamented	Polymorphonuclears: Eosinophils	Polymorphonuclears: Basophils	Lymphocytes: Large	Lymphocytes: Small	Monocytes	Eosinophils, per Cu. Mm.	Comment
7/7	½ tablet, 11:30 a.m.	8:00	5.11	86	= 11.8	340,000	8,600	40	2	8	2	4	0	8	688	
		1:30				310,000	11,700	50	3	7	..	3	2	8	819	
		2:30				390,000	9,100	56	3	7	..	3	0	4	637	
		3:30				290,000	7,000	50	7	7	..	3	0	6	490	
		4:30				260,000	8,100	53	4	11	..	2	2	10	891	
		6:00				250,000	10,800	58	4	5	1	2	5	7	540	
7/8	1 tablet, 10 a.m.	8:00	5.08	86		300,000	9,000	41	6	5	..	3	8	10	450	Plasma vitamin C, 0.67 mg. per 100 cc.
		12:00				190,000	7,800	51	10	6	..	3	0	3	468	
		1:00				210,000	7,600	50	5	11	..	2	8	6	836	
		2:00				200,000	8,900	54	10	8	1	2	2	5	712	
		4:00				210,000	8,600	45	5	7	..	4	0	3	602	
		6:00				210,000	9,300	46	8	5	..	3	5	6	465	
7/9	1 tablet, 11 a.m.	8:00	5.16	86		230,000	7,500	40	5	10	..	3	4	11	750	Plasma vitamin C, 0.74 mg. per 100 cc.
		1:00				180,000	9,100	62	4	6	..	2	2	6	546	
		3:00				170,000	8,900	38	2	10	..	4	4	6	890	
		5.00				180,000	8,100	42	3	11	1	3	8	6	891	
7/10	2 tablets, 8:45 a.m.	8:00	5.32	86		240,000	8,500	43	6	7	..	3	6	8	595	
		10:45				200,000	9,050	40	7	6	..	4	2	5	543	
		1:00				150,000	8,850	45	1	4	..	4	4	6	354	
		3:00				170,000	8,600	48	4	8	..	3	6	4	688	
		5:00				150,000	8,100									
		8:00				160,000	9,300	40	4	6	..	4	2	8	588	
7/11	2 tablets, 9:30 a.m.	8:00	5.22	86		180,000	10,100	44	4	6	..	4	0	6	606	Plasma vitamin C, 1.11 mg. per 100 cc.
		11:30				230,000	8,700	43	8	6	..	3	3	10	522	Bleeding time, 25 min.
		2:00				210,000	8,900	48	3	6	..	3	7	6	534	
		4:00				160,000	8,700	44	7	6	..	4	0	3	522	
		6:00				150,000	9,100	36	4	5	1	4	8	6	455	
		8:00				160,000	8,800									
7/12	2 tablets, 9 a.m.	8:00	5.11	86		130,000	9,200	38	6	6	1	3	9	10	552	Plasma vitamin C, 1.11 mg. per 100 cc.

		11:00			130,000	9,700	42	12	6	..	3	0	10	592	
		1:00			130,000	8,900	36	6	12	..	4	0	6	1,086	
		3:00			130,000	8,300	53	3	7	..	3	1	6	581	
	½ tablet, 6 p.m.	5:00			110,000	8,050	42	12	6	..	3	2	8	483	
7/15	½ tablet, 9 p.m.	8:00	5.05	86	100,000	7,100	28	18	6	..	3	4	14	426	Plasma vitamin C, 1.32 mg. per 100 cc.
		11:00			100,000	7,050	46	14	6	..	2	6	8	423	
		2:00			80,000	7,300	46	6	7	..	3	2	8	511	
		4:00			80,000	7,700	32	10	9	..	4	2	7	693	
	½ tablet, 7 p.m.	6:00			80,000	7,500	34	6	8	1	4	0	11	600	
7/14	½ tablet, 9 a.m.	8:30	5.19	88 = 12.06	80,000	6,700	40	4	10	..	3	7	9	670	Plasma vitamin C, 1.05 mg. per 100 cc.
		11:00			80,000	7,000	40	10	6	..	4	0	4	420	Bleeding time, 2 min.
		1:00			80,000	6,700	40	9	4	..	3	4	13	268	Coagulation time, 4 min.
		3:00			80,000	7,300	36	4	7	..	4	7	6	511	Clot retraction good
	1 tablet, 10 p.m.	7:30			80,000	10,100	32	8	4	2	4	2	12	404	
7/15		8:30	5.08	88	65,000	7,900	46	0	7	..	3	7	10	553	Bleeding time, 2 min.
		11:00			70,000	7,700	52	4	6	..	3	6	2	462	
		1:00			70,000	8,000	52	4	4	..	3	5	4	356	Clotting time, 6 min.
		5:00			70,000	7,100	38	4	9	1	3	2	16	639	No clot retraction
7/16	.....	8:00	5.11	88	55,000	6,400	36	4	8	1	4	6	4	512	
		10:30			63,500	6,700	42	6	7	1	3	8	6	469	
		12:30			70,000	6,400	44	6	4	..	3	6	10	512	
		2:30			75,000	6,500	44	4	5	..	3	8	9	325	
		5:00			78,000	6,700									
7/17	.....	12:00			130,000	8,050	48	6	8	..	2	4	14	644	
		7:00			140,000	8,200	60	10	6	1	1	7	6	492	
7/18	.....	8:30	5.17	88	190,000	8,300	..	..	..	..	..	..	..	...	Plasma vitamin C, 1.20 mg. per 100 cc.
		1:00			200,000	8,600	56	8	5	..	2	7	4	430	
		5:00			290,000	8,300									
7/19	.....	8:30	5.08	88	320,000	6,900									
7/25	.....	.....	5.18	88	460,000	7,900									

* Note time required for return to the normal platelet level when no vitamin C therapy was used.

millimeter or below, larger forms appeared. Some were about one half the size of a red blood cell. As the platelet count rose, after cessation of administration of sedormid, there appeared to be a tendency for aggregation of platelets on the films.

On July 7 before any sedormid was given, aspiration of the marrow of the sternum was performed. This procedure was repeated on July 15, when the platelet count was 70,000 per cubic millimeter, and after several purpuric spots had appeared in the skin over various portions of the body. The results were:

	July 7	July 15
Myeloblast	5	5
Promyelocyte	1	1
Myelocytic neutrophil	12	12
Myelocytic eosinophil	3	6
Metamyelocytic neutrophil	23	17
Metamyelocytic eosinophil	3	7
Polymorphonuclear neutrophil	22	18
Polymorphonuclear eosinophil	4	2
Lymphocyte	3	4
Megakaryocyte	1	3
Proerythroblast	4	9
Erythroblast (including normoblast)	19	16

On July 15 the platelets in the marrow films were markedly reduced in number and tended to be larger than normal (4 to 6 microns in diameter).

Table 2 shows that no parallel increase in the number of eosinophils accompanied leukopenia and a drop in the number of platelets, which has been said to occur in food allergy, and there was no leukopenia with granulocytopenia, which has been stated to occur in persons sensitive to aminopyrine and allied drugs. This table does show an average rise above normal in the number of eosinophils (also shown in fig. 3), which we attributed to the allergic state causing the attacks of asthma and hay fever.

It will be noted that the percentage of vitamin C in the blood plasma of the patient was slightly lower on July 8, 1938 than on June 21, 1937, at the time of her first entry. The values for vitamin C in the plasma gradually rose during the time of the second experiment (July 7 to 19, 1938). This occurred in the absence of parenteral or oral administration of vitamin C other than that included in her diet. We are unable to interpret the significance of this rising percentage of vitamin C in the plasma during the second experiment, unless the low amount, 0.67 mg. per hundred cubic centimeters, on admission (July 8) was the result of a diet inadequate in vitamin C before the patient came to the hospital.

SUMMARY

No definite evidence was found that vitamin C, by either oral or parenteral administration, diminished the intensity of the purpuric lesions and hemorrhagic manifestations of the patient reported, nor did it shorten the period necessary for recovery from these manifestations.

This patient was apparently only slightly sensitive to sedormid and was less sensitive after the lapse of a year, during which time she had not taken any sedormid. Differential cell counts and study of the marrow of the sternum, both before and after the induced attack of purpura, showed stimulation of the early granulocyte elements, i. e.,

myeloblasts, myelocytes and metamyelocytes. The erythroid elements were increased, probably as part of a stimulation of granulocytes and erythropoietic elements. The megakaryocytes were not increased in either of the two counts.

The formed elements of the peripheral blood other than the platelets showed very slight, if any, change during either experiment. We have a careful record of daily blood counts during the entire period of the experiments, but did not include all of them because of a desire to conserve space.

AN EPIDEMIC DISEASE OF THE RESPIRATORY TRACT

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In the past few years numerous clinicians have described isolated cases and epidemics of infection of the respiratory tract especially associated with pulmonary involvement. The disease in most instances resembled epidemic influenza so closely that clinical differentiation could not be made, and in only one or two studies were attempts made to differentiate the disease from influenza by serologic or other laboratory methods. Definite diagnoses in this group of infections of the respiratory tract cannot be made, of course, until the etiologic agents in the different diseases become known.

Various names have been given to the diseases described, such as acute pneumonitis,[1] acute influenza pneumonitis,[2] acute interstitial pneumonitis,[3] atypical pneumonia,[4] bronchopneumonia,[5] pseudolobar-bronchopneumonia,[6] benign circumscribed pneumonia,[7] disseminated focal pneumonia,[8] acute diffuse bronchiolitis [9] and capillary pneumonia.

From the Department of Medicine, Jefferson Medical College Hospital.

Presented in part with Dr. Joseph Stokes Jr. before the Association of American Physicians, Atlantic City, N. J., May 2, 1939.

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2. Bowen, A.: Acute Influenza Pneumonitis, Am. J. Roentgenol. **34**:168-174 (Aug.) 1935.

3. Smiley, D. F.; Showacre, E. D.; Lee, W. F., and Ferris, A. W.: Acute Interstitial Pneumonitis: A New Disease Entity, J. A. M. A. **112**:1901-1904 (May 13) 1939.

4. Cass, J. W.: The Question of "Influenza" and Atypical Pneumonia, New England J. Med. **214**:187-193 (Jan. 30) 1936.

5. Miller, F. N., and Hayes, M. G.: Bronchopneumonia of Mild Severity at the University of Oregon, Northwest Med. **38**:12-14 (Jan.) 1939.

6. Jeanneret, R., and Famé, F.: L'image radiologique de la bronchopneumonie grippale, Rev. méd. de la Suisse Rom. **51**:418-422 (June 10) 1931.

7. Ramsay, H., and Scadding, J. G.: Benign Broncho-Pulmonary Inflammations Associated with Transient Radiographic Shadows, Quart. J. Med. **32**: 79-95 (April) 1939.

8. Scadding, J. G.: Disseminated Focal Pneumonia, Brit. M. J. **2**:956-959 (Nov. 13) 1937.

9. McKinlay, C. A.: Acute Diffuse Bronchiolitis, with Report of a Case, Journal-Lancet **59**:90-91 (March) 1939.

These terms may be fairly descriptive of the underlying pathoanatomic changes, but beyond this they serve no useful purpose. Furthermore, in our recent experience with a disease to be described, all of these terms were too restrictive, since they are applicable only in the minority of cases of the severe form with pneumonia in an epidemic in which the lungs were seldom involved (fig. 2).

In the spring months of 1938, 8 cases of a severe form of atypical pneumonia were studied at the Jefferson Medical College Hospital.[10] Several more occurred among the hospital personnel in August, November and December. During this time the number of cases of mild infection of the respiratory tract was not unusual, and in only 1 instance did it appear to be related to the severe form. Because of the peculiar nature of the disease, attempts were made to determine the etiologic agent.[11] From 2 patients a filtrable infectious agent was recovered which when inoculated into animals caused bacteria-free pneumonia, characterized by an inflammatory reaction of the interstitial tissue of the lungs with a mononuclear cell exudate and often encephalitis. Unfortunately, the agent disappeared during passage in animals, and proof of its etiologic relationship to the disease was not established. Nevertheless, because of this suggestive evidence and the clinical resemblance of the disease to other known virus infections of the respiratory tract, it was suggested that a virus was the cause.

During the same season of 1938 many sporadic cases and epidemics of disease strikingly like the one described here were observed in Ohio, Delaware, Oregon, New York, Minnesota, Missouri[12] and elsewhere, giving reason to believe that a special infectious agent was common to all.

EPIDEMIC OF 1939

Sporadic cases of an unusual form of pneumonia were observed in the Jefferson Hospital, as stated, until late in 1938, but in January 1939 an epidemic of a mild disease of the respiratory tract began in Philadelphia, which reached widespread proportions in February.[13] In our experience it was the most widespread epidemic of many years.

10. Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia: A Disease Entity Probably Caused by a Filtrable Virus, J. A. M. A. **111**:2377-2384 (Dec. 24) 1938.

11. Stokes, J.; Kenney, A. S., and Shaw, D. R.: A New Filtrable Agent Associated with Respiratory Infections, Tr. Coll. Physicians Philadelphia **6**:329-333, 1939.

12. Miller, M. E.; Wingfield, P. B.; Harrington, F. E.; Langmuir, A. D., and Edwards, J. C.: Personal communication to the authors.

13. Reimann, H. A., and Stokes, J., Jr.: An Epidemic Infection of the Respiratory Tract in 1938-1939, Tr. A. Am. Physicians **54**:123-129, 1939.

Similar outbreaks, with a high morbidity rate, were reported from New York, Minnesota, Illinois, England,[14] France and elsewhere at about the same time. In some places schools were closed in an effort to stop the spread of the disease, and other localities were apparently not affected at all. Since most patients were not ill enough to seek medical aid, it was impossible to learn the real extent of the pandemic, so that its incidence is not accurately reflected in the statistics of city and state health departments. Furthermore, the mild form may be confused with true influenza or similar infections, and the severe form with pneumonia may be mistaken for the pneumonias of bacterial origin.

It would be important to know whether the disease observed in 1938 was caused by the same agent as that of 1939. There is reason to believe that it was, because of the clinical similarity of both the mild and the severe type in the two outbreaks, but many more cases of the mild than of the severe form occurred in 1939. This behavior is similar to that of epidemic influenza in 1918-1919. Numerous isolated cases of a severe infection of the respiratory tract occurred a year or two before the outbreak of the great pandemic.[15]

CLINICAL STUDIES

Since it was thought that a study of the epidemic in a more or less "closed" and easily controlled group of persons would be of value in describing the disease, our observations were limited chiefly to the interns, nurses and medical students comprising a group of 813 persons at Jefferson Medical College and Hospital. Of this group, 407 persons, or 50 per cent, were ill presumably of the same disease. Of the 407 persons affected, only about 100 were ill enough to be admitted to the hospital for treatment. The date of onset of the illness in these patients is shown in figure 1.

It was not possible to measure the period of incubation because of the numerous possibilities of exposure. We believe the incubation period was short, perhaps one or two days, but others have suggested it to be two weeks.

The disease was primarily an inflammation of the mucous membranes of the respiratory tract, usually of the nose, pharynx and larynx, occasionally including the trachea and bronchi, and in a few cases the bronchioles and lungs. Constitutional symptoms were usually in proportion to the extent and intensity of the mucosal inflammation. The

14. Andrewes, C. H.: Epidemic Influenza, Lancet **1**:589-590 (March 11) 1939.

15. Hammond, J. A. B.; Rolland, W., and Shore, T. H. G.: Purulent Bronchitis, Lancet **2**:41-45 (July 14) 1917. Abrahams, A.; Hallows, N. F.; Eyre, J. W. H., and French, H.: Purulent Bronchitis: Its Influenzal and Pneumococcal Bacteriology, ibid. **2**:377-382 (Sept. 8) 1917.

clinical course was remarkably uniform in most cases, differing chiefly in degree of severity. For simplicity in discussion, the cases were classified as those of mild (ambulatory patients), moderately severe (bedfast patients) and severe forms.

Mild Form.—By far the largest proportion of the 407 patients (307, or 75 per cent) were ambulatory. Their illnesses perhaps would

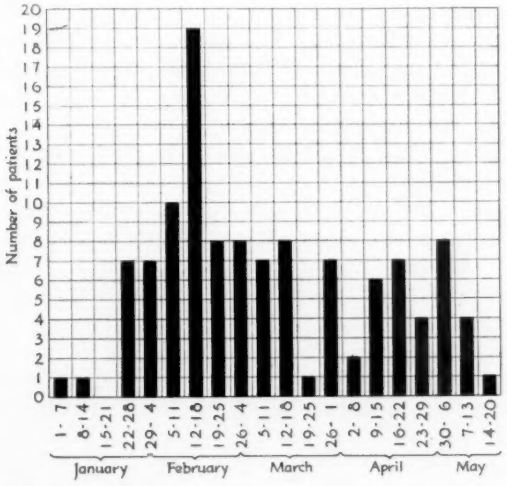

Fig. 1.—Weekly incidence of cases of the moderately severe and severe form in the epidemic.

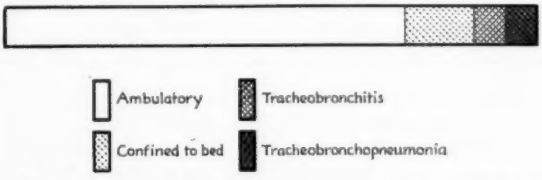

Fig. 2.—Relative proportion of ambulatory patients (75 per cent) and patients confined to bed (25 per cent). Twelve per cent of all patients had tracheobronchitis, and 6 per cent had pneumonia.

ordinarily be regarded as unimportant "colds," but because of the coincidence with other more severe, but clinically similar, infections, we have regarded them as part of an epidemic of a single disease entity (fig. 2). These persons usually complained of coryza, obstruction of the nose, malaise, frontal headache, weakness, dizziness, sweating and anorexia. Rhinorrhea and lacrimation were rare, but the conjunctivas

were often injected. There was occasional dry cough, but rarely fever. The illness lasted from one to several days. A number of persons had one or two relapses, which in some cases were severe.

Moderately Severe and Severe Forms.—About 100, or 25 per cent, of those who were sick had to go to bed. Of this number, 25 had tracheobronchitis and 25 had tracheobronchopneumonia. The onset in most cases (97 per cent), as in those of the mild form, was insidious. Headache, dry or mild sore throat, coryza, malaise, muscular pains, cough and shivering were the most frequent complaints, in the order named. In a day, or after several days, these symptoms increased in severity. Aching, backache, frontal headache, pain in the eyeballs, photophobia, malaise and sweating were present in over 80 per cent of cases. Over 70 per cent of patients had persistent hacking or paroxysmal cough, which often interfered with sleep. Only 27, however, raised sputum, but never more than 30 cc. a day. Sixty patients complained of dry, raw or sore throat, and hoarseness with aphonia developed in 4. A few patients with intensely inflamed throats were surprisingly free from local discomfort. Catarrhal or exudative symptoms were rare. Of the abdominal symptoms, anorexia (52 cases) and muscular soreness from coughing (16 cases) were most frequent; vomiting and diarrhea were present in 12 instances.

The severity of the illness was generally in proportion to the extent and intensity of the inflammation of the mucous membranes. Most of the severely ill patients had evidence of tracheobronchitis or pneumonia, but a few without pulmonary invasion felt worse than those with it, but for a shorter time. Hoarseness and aphonia were more common in those with pulmonary invasion, as were drenching sweats and weakness. Fever lasted on an average two and a half days in patients without involvement of the lungs, four and six-tenths days in those with tracheobronchitis and eight and two-tenths days in those with pneumonia.

Physical Signs.—The patients often looked ill; the face was flushed, and the eyes were reddened. The most constant feature of the moderately severe form (92 per cent of cases) was the inflamed mucous membranes of the upper portion of the respiratory tract. According to Dr. Calvin Fox, who examined each of these patients, the mucous membranes, particularly the lymphoid tissue, of the nose, oropharynx and pharynx, and frequently the larynx, including the epiglottis, arytenoid cartilages and vestibule, and the trachea were intensely red and dry, with varying degrees of congestion. Occasionally the congestion in the nose was sufficient to obstruct breathing. In the severely sick patients, crusting with excoriations resembling pinpoint hemorrhages were observed on the nasal septum. In a few cases the vocal cords were inflamed and thickened. Little or no exudate was found in the nose,

but small quantities of tenacious mucopus were sometimes present in the oropharynx. Cervical lymphadenopathy was rarely observed.

The severe cough of most patients suggested tracheal, bronchial or pulmonary involvement, but in only 4 patients with tracheobronchitis who did not have frank pneumonia were rales or suppressed breath sounds heard in the hilar areas of the lungs. In 23 of 86 cases roentgenograms made by Dr. Karl Kornblum showed evidence of tracheobronchitis (fig. 3) in the absence of physical signs, a fact emphasized by others (Scadding).[5] Three patients were regarded as having tracheobronchitis in the absence of roentgenographic evidence because of rales in the interscapular areas. Evidence of pneumonia was present as indicated by abnormal physical signs and roentgenographic findings in 25 patients. The roentgenographic features will be the subject of a separate paper.

The temperature was usually elevated and averaged from 38.3 to 39.5 C. (101 to 103 F.), and the pulse rate was increased in proportion

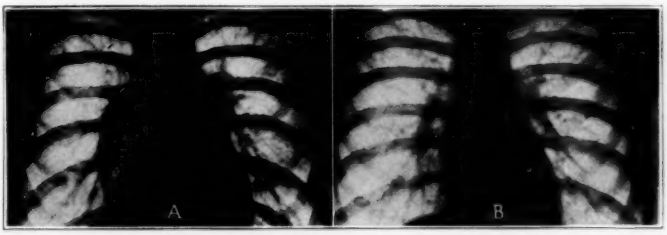

Fig. 3.—Roentgenograms in a case of tracheobronchitis. The patient had been ill for three days with symptoms of the moderately severe form with nasopharyngitis. There was little cough or sputum and no abnormal physical signs in the lungs. *A*, made during the illness, shows generalized increase in the pulmonary markings in both lungs, indicating acute tracheobronchitis; in *B*, made five days later, the shadows are less prominent.

to between 110 and 120. The respiratory rate was occasionally increased. The clinical record in a typical case is given in figure 4. The sputum, when present, was occasionally blood tinged, but otherwise was not characteristic. The number of leukocytes in the blood ranged between 5,000 and 8,000 per cubic millimeter, often with a slight increase in the proportion of polymorphonuclear cells. The sedimentation rate of the erythrocytes was usually increased.

Patients with Pneumonia.—Pneumonia developed in 25 patients. There were 8 cases of pneumonia among 38 interns. The onset was usually insidious, like that already described, but signs of spread to the lungs appeared after several days or a week or more had elapsed. In

several cases signs of pneumonia were present in the first few days. The clinical picture in general was similar to that described before,[10] and need not be given in detail again. Outstanding features were nasopharyngolaryngitis, tracheitis and bronchitis of varying degrees of extent and severity; paroxysmal cough; minimal amounts of exudate and sputum; frontal headache; aching of the eyes, photophobia; slight cyanosis; dyspnea, and frequently profuse sweating. There were occasional dulness and suppressed breath sounds; invariably rales were present in one or both interscapular areas, but sometimes were confined to one lobe, or were heard in several lobes at the same time or in succession. Weak bronchophony or egophony was occasionally heard. Roentgenograms almost always showed localized or diffuse areas of

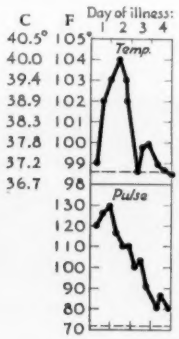

Fig. 4.—Temperature and pulse rate in a case of moderately severe respiratory infection with nasopharyngotracheobronchitis in a nurse aged 20. She felt well until February 9, when onset occurred with malaise, chilliness, fever, sweating, headache, backache, aching of the eyeballs and a dry, harsh, nonproductive cough. Some soreness and pain in the left axilla were noted. The patient was hoarse; her face was flushed, and the eyes were reddened. The mucosa of the nose and throat was swollen, dry and reddened. The lymph follicles in the pharynx were particularly inflamed and swollen, and the visible blood vessels were distended. The chest was normal except for suppressed breath sounds in the lower lobe of the right lung posteriorly; a roentgenogram showed generalized increase in the pulmonary markings, particularly in both hili. The leukocyte count was 5,000. Cultures made of the pharyngeal exudate showed Str. viridans in predominance, Str. haemolyticus, N. catarrhalis, Staphylococcus albus and diphtheroids. General aching of the limbs, nausea and vomiting occurred on the second day, but convalescence thereafter was rapid.

density where abnormal signs were found (fig. 5). In 3 cases shadows of pulmonary invasion were present without physical signs, and in 4 cases physical signs were present without shadows in the roentgenograms.

Relative bradycardia was noted only in the cases of severe disease with pneumonia of long duration. Fever was continuously high or occasionally remittent, and the temperature declined by lysis (fig. 6). The disease with pneumonia lasted from two to seventeen days, with an average of eight and two-tenths days. Often there was loss of weight of 5 to 10 Kg. (11 to 22 pounds). All the patients recovered. Convalescence was usually rapid, but was prolonged in several cases by weakness and sweating. In a number of cases relapse, with mild nasopharyngitis, occurred after several weeks. The number of leukocytes was usually normal or slightly increased toward the end of the illness. The sedimentation rate of the erythrocytes was increased, especially late in the disease. All cultures of the blood were sterile. In similar cases in New York city, Chickering [16] noted a marked increase in the number of mononuclear cells in the sputum.

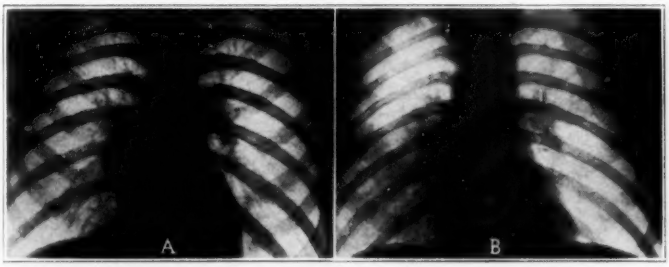

Fig. 5.—Roentgenograms in a case of tracheobronchopneumonia charts for which appear in figure 6. *A*, taken on the second day of the disease, shows intensification of hilar shadows, especially on the right; *B*, taken on the eighth day, shows a diffuse, mottled shadow in the middle and lower lobes of the right lung. On the thirteenth day a faint shadow appeared in the hilar area of the lower lobe of the left lung.

OTHER MANIFESTATIONS

As in many other infectious diseases, we believe that in some instances organs and tissues other than the respiratory tract may be affected. In 1938 the cases of 2 patients with symptoms of encephalitis were mentioned.[10] In the group studied in 1939, 4 persons had many of the typical signs and symptoms described, but were much more troubled by general abdominal cramps, watery diarrhea, anorexia, nausea and vomiting. The illness lasted several days in each case, left the patient weak and caused the loss of from 2 to 5 Kg. (5 to 10 pounds) in weight.

16. Chickering: Personal communication to the authors.

In 3 medical students whose signs and symptoms warranted inclusion of their cases in the epidemic, jaundice developed five to seven days after the beginning of the symptoms of nasopharyngitis. The clinical course was then typical of the disease commonly known as catarrhal jaundice. Whether this syndrome and gastroenteritis were both caused by the same infectious agent is of course uncertain, but since no similar conditions developed in the group studied either before or after the epidemic they were presumably a part of the disease.

Relapse or recrudescence of the disease occurred in 17 patients of the group. Relapses were more severe than the preceding attack in some and less severe in others. Here, again, it is uncertain whether relapses

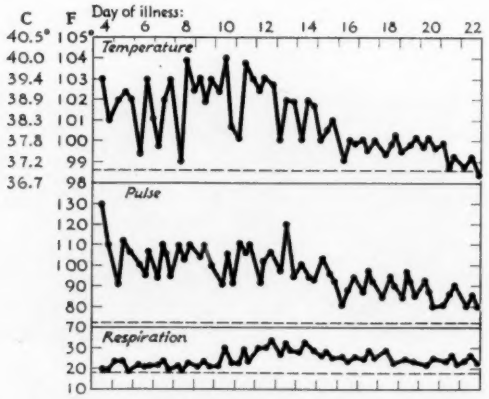

Fig. 6.—Severe infection of the respiratory tract with nasopharyngotracheobronchopneumonia in an intern aged 25, who had had a slight cold with obstruction of the nose and injection of the conjunctivas for several days. On January 24, a rather abrupt onset of dry, wracking cough, substernal soreness, malaise, general aching, photophobia, chilly sensations, fever and sweating was noted. The nasopharynx was inflamed. The leukocyte count was 8,600. Ferrets were inoculated with nasopharyngeal washings on January 24. Two days later the patient's throat was sore, and hoarseness developed. There was slight suppression of breath sounds in the base of the right lung posteriorly, and rales were heard the next day. Herpes appeared on the lips, and paroxysms of cough were severe. Several days later dyspnea and cyanosis required oxygen for relief. The respiratory rate was not greatly increased, in spite of dyspnea and cyanosis, which appeared about the second week. Tachycardia was present early in the course, followed by relative bradycardia. Nasopharyngitis, photophobia and sweating persisted for ten days. Rales were heard in the base of the left lung on the thirteenth day. The leukocyte count was 14,000. Rales and hoarseness persisted until the twenty-first day. Roentgenograms are shown in figure 5. Loss of weight was 8.2 Kg. (18 pounds). Convalescence was slow but uneventful.

were caused by the same agent as that in the first attack, by a biologic modification of it or by a different agent, but because of similar clinical features the relapses were regarded as being due to the same cause.

COMPLICATIONS

There were no important complications among our patients except gastroenteritis and jaundice, which may not be complications at all, but a part of the disease itself. In 5 cases, after several days of the mild symptoms as described, typical acute follicular tonsillitis with leukocytosis developed. A pure culture of hemolytic streptococci was recovered from the exudate on the tonsils. Maxillary sinusitis developed in 2 cases. In several patients not included in the group studied, but admitted to the general medical service of the hospital, typical lobar pneumonia caused by pneumococci of types I, II and VII developed after an illness of several days or a week with nasopharyngotracheitis, presumably of the kind described here.

ETIOLOGIC STUDIES

As in the previous year, when a filtrable agent was recovered from 2 patients,[11] anesthetized ferrets were inoculated intranasally by Dr. Joseph Stokes Jr. and Mrs. Shaw with nasopharyngeal secretions taken from 11 patients early in the course of the disease. Aside from demonstrating the absence of the virus of epidemic influenza, no decisive results were obtained. In a few instances the animals appeared to be ill after inoculation, but on further passage no evidence of disease developed. Complement fixation tests with influenza virus as antigen made on the blood of 15 patients gave negative results.

Bacteriologic studies of sputum and nasopharyngeal exudates showed the presence of Streptococcus viridans, Streptococcus haemolyticus, Neisseria catarrhalis, diphtheroids and staphylococci, named in the order of frequency. None was considered to be of etiologic importance. Bacillus influenza was not encountered. There was also a remarkable scarcity of pneumococci. They were recovered in only 6 cases, usually from the sputum and rarely from pharyngeal swabs, which had to be made in most cases because of the absence of sputum. Exudate was routinely injected into mice, but only pneumococci of types IV, VIII, XVIII and XXIX and two unclassified strains were isolated. They were not regarded as etiologically significant.

TREATMENT

No active treatment was used in cases of the mild form. Patients were advised to remain in bed, but seldom did so. Patients with moderately severe attacks went to bed. They were usually kept isolated in

separate rooms. Headache and aching were controlled with codeine sulfate, 0.03 to 0.06 Gm. (½ to 1 grain) by mouth, as needed. An ice cap to the head was often comforting. Acetylsalicylic acid, acetophenetidin and aminopyrine were seldom used because of the diaphoresis they cause, which in many cases was an annoying symptom of the disease itself. Cough was often relieved by menthol cough lozenges or by steam from a water vaporizer. For severe cough codeine was given to permit sleep. Pain in the abdominal muscles from coughing was relieved by a snugly fitting binder. Oxygen was helpful only when dyspnea and cyanosis were present. The bowels were kept open with mild laxatives and enemas as needed, and the diet was unrestricted, except for patients with nausea, vomiting or diarrhea.

Swabs and applications to the mucous membranes of the nose and throat were found to cause discomfort and were generally not used. A spray of physiologic solution of sodium chloride or a weak solution of sodium perborate as a gargle often relieved the sense of dryness in the nose and throat. An aqueous spray containing a 1 per cent solution of ephedrine hydrochloride or epinephrine hydrochloride was used to relieve nasal obstruction.

The question of chemotherapy and specific antipneumococcus serum therapy was raised in several of our cases in which pneumococci were present in the sputum, but not in the blood. In a few cases, in spite of the atypical nature of the pneumonia, both sulfapyridine and serum were given, but the absence of a prompt response suggested that the pneumococci present had no etiologic significance. Sulfapyridine given alone to certain patients had no beneficial effect and usually caused discomfort, with nausea and cyanosis. Several patients in the general medical service of the hospital in whom typical pneumonia due to Pneumococcus types I, II and VII subsequently developed, were promptly benefited by sulfapyridine and specific antipneumococcus serum.

COMMENT

The epidemic disease of the respiratory tract reported was considered to be an etiologic entity clinically similar to epidemic influenza, but caused by a different agent. The disease occurred in varying degrees of severity, from the mildest forms with inflammation of the nose and throat, of a few days' duration, to the severe forms with pulmonary involvement, often lasting several weeks. Cases of the mild form far outnumbered those of the severe form, and for this reason we believe it to be misleading to apply restrictive names indicating special forms of bronchiolitis or pneumonia to cases of the severe form alone, as many have done. It should be recognized that, as in the case of influenza, both mild and severe forms may be due to

the same cause without the agency of bacteria, although bacteria may eventually invade the damaged lung.[17] From the standpoint of public health mild infections are all potentially dangerous. They may be the precursors of an outbreak of a more serious epidemic disease of the respiratory tract caused by the invasion of bacteria, like that which occurred in 1918-1919 after influenza. Fortunately, in the winter of 1939 either the mild disease did not favor bacterial invasion or highly invasive organisms, such as pneumococci, hemolytic streptococci, staphylococci or Pfeiffer's bacilli, were not as prevalent as usual, and the mortality rate in our group of patients was nil.

Differential Diagnosis of the Philadelphia Epidemic of 1939, Epidemic Influenza and Febrile Catarrhs *

	Epidemic Influenza	Febrile Catarrhs	Philadelphia Epidemic of 1939
Onset	Sudden	Insidious	Insidious
Symptoms	Constitutional symptoms preponderant	Respiratory symptoms preponderant	Constitutional symptoms preponderant
Cough	Short and dry	Paroxysmal, irritating, painful, often productive	Paroxysmal, hacking, nonproductive
Voice	Husky	Hoarse	Husky or hoarse
Throat	Posterior pharyngitis; no exudate	Tonsillitis as well as pharyngitis; exudate common	Nasopharyngolaryngitis; no exudate
Fever	Sometimes diphasic	Rarely diphasic	Rarely diphasic
Complications	Bronchiolitis and pneumonia	Bronchitis or bronchopneumonia	Tracheobronchopneumonia considered part of the disease, not a complication
Epidemic	Short, with rapid "peaking"	Prolonged and "grumbling"	Prolonged
Contacts	Clinical picture uniform, although graded in severity	Clinical picture variable, with frank tonsillitis in contacts	Clinical picture uniform, although graded in severity
Leukocyte count	Not diagnostic	Not diagnostic	Not diagnostic
Virus	Influenza virus recoverable from pharynx	Influenza virus not concerned	Influenza virus not concerned

* The differentiation was based on the criteria of Stuart-Harris and his associates.[18]

It is interesting to apply to the disease described the clinical criteria proposed by English observers for the differentiation of epidemic influenza from the "febrile catarrhs." [18] In general the disease we describe fits more closely the pattern of influenza; yet certain important differences exist as shown in the accompanying table, chief of which are the absence of the virus of influenza, the insidious onset, the paroxysmal

17. Scadding, J. G.: Lung Changes in Influenza, Quart. J. Med. **6**:425-465 (Oct.) 1937.

18. Stuart-Harris, C. H.; Andrewes, C. H.; Smith, W.; Chalmers, D. K. M.; Cowen, E. G. H., and Hughes, D. L.: A Study of Epidemic Influenza, with Special Reference to the 1936-1937 Epidemic, Medical Research Council, Special Report Series, no. 228, London, His Majesty's Stationery Office, 1938.

cough, sweating and the epidemiologic features. The disease differs from the febrile catarrhs chiefly in the constitutional symptoms, the paucity of exudate and the uniform clinical picture.

It is probable that the disease is the same as, or similar to, that described by other investigators in 1938-1939, but one cannot assume its identity with the forms described in previous years without further evidence, since few attempts at differentiation with biologic methods were made. In some of these cases the disease may have been true influenza, and in some, other entities. It is probable that a group of numerous infections may cause disease of the respiratory tract of which the present one is a member. Only by the perfection of methods of identifying the causative agents can they finally be separated into specific entities.

Diagnosis in cases with the form of pneumonia described here is not difficult when many cases occur in an epidemic of similar infections, both of the mild and the severe type. Isolated cases may be difficult to recognize, and in our first experiences [10] psittacosis, typhoid fever and pulmonary tuberculosis were often considered. The possibility of secondary bacterial invasion and pneumonia caused by the ordinary varieties of bacteria must always be kept in mind.

The disease should perhaps be given a temporary general name, such as grip (as dissociated from true influenza), until the etiologic agent is discovered. Many features of the disease, such as its epidemiology, the close resemblance to other diseases known to be caused by filtrable viruses, the normal leukocyte count and the absence of evident causative bacteria, suggest to us that a filtrable virus is the cause, but proof is wanting.

SUMMARY

An epidemic disease of the respiratory tract occurred in Philadelphia and elsewhere in the winter of 1939. Reports of similar outbreaks in many parts of this country and in Europe suggest that it may have been pandemic. Of a group of 813 persons in the personnel of the Jefferson Medical College and Hospital, 50 per cent were ill. The majority of patients (88 per cent) were ill with nasopharyngolaryngitis. Six per cent had tracheobronchitis in addition, and 6 per cent had tracheobronchopneumonia. In most of the severely ill patients the lungs were presumably involved by the infectious agent suspected, without the agency of the usual varieties of bacteria. There were no serious complications, and all the patients recovered. The disease resembles epidemic influenza in many respects, but it is caused by a different agent. It represents a clinical entity probably caused by a filtrable virus.

EFFECT OF RENAL RETENTION OF VITAMIN C ON SATURATION TESTS

A FORMULA FOR COMPENSATION OF THIS FACTOR OF ERROR

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NEW YORK

In 1933, Harris, Ray and Ward[1] demonstrated the excretion of vitamin C in the urine and established a relationship between the excretion and the intake of this vitamin. Since that time, a number of chemical methods for the determination of the state of vitamin C nutrition in man have been presented. The determination of the twenty-four hour "resting level" of urinary excretion presented many technical disadvantages and was impractical in the study of ambulatory patients. The content of ascorbic acid in the fasting blood was observed to vary considerably with the recent dietary intake of vitamin C and gave only a rough index of the actual state of saturation.[2] The test dose method, in which a given dose of ascorbic acid is administered and the output in the urine is used as an index of saturation, was found to have many advantages. Oral test doses of 300 to 1,000 mg. were first used.[3] The

From the Department of Medicine of the New York Post-Graduate Medical School and Hospital.

This study was aided by a grant from Merck & Co., Inc., Rahway, N. J., who also furnished the ascorbic acid used.

1. Harris, L. J.; Ray, S. N., and Ward, A.: The Excretion of Vitamin C in Human Urine and Its Dependence on the Dietary Intake, Biochem. J. **27**:2011, 1933.

2. (*a*) Wright, I. S.: The Present Status of the Clinical Use of Cevitamic Acid (Ascorbic Acid) (Crystalline Vitamin C), Am. J. M. Sc. **192**:719, 1936. (*b*) Greenberg, L. D.; Rinehardt, J. F., and Phatak, N. M.: Studies on Reduced Ascorbic Acid Content of the Blood Plasma, Proc. Soc. Exper. Biol. & Med. **35**:135, 1936. (*c*) Portney, B., and Wilkinson, J. E.: Vitamin C Deficiency in Peptic Ulceration and Hematemesis, Brit. M. J. **1**:554, 1938.

3. (*a*) Johnson, S. W., and Zilvd, S. S.: Urinary Excretion of Ascorbic and Dehydro-Ascorbic Acids in Man, Biochem. J. **28**:1393, 1934. (*b*) Abbasy, M. A.; Harris, L. J.; Ray, S. N., and Marrack, J. R.: Diagnosis of Vitamin-C Subnutrition by Urine Analysis: Quantitative Data—Experiments on Control Subjects, Lancet **2**:1399, 1935. (*c*) Youmans, J. B.; Corlette, M. B.; Akeroyd, J. H., and Frank, H.: Studies of Vitamin C Excretion and Saturation, Am. J. M. Sc. **191**:319, 1936. (*d*) Harris, L. J.; Abbasy, M. A., and Yudkin, J.: Vitamins in Human Nutrition: Vitamin C Reserves of Subjects of the Voluntary Hospital Class, Lancet **1**:1488, 1936. (*e*) Goldsmith, G. A., and Ellinger, G. F.: Ascorbic Acid in Blood and Urine After Oral Administration of a Test Dose of Vitamin C: Saturation Test, Arch. Int. Med. **63**:531 (March) 1939.

large factor of error due to the variability of absorption and utilization from the gastrointestinal tract was eliminated by the intravenous administration of the test doses.[4] A five hour test, after the intravenous injection of 1 Gm. of ascorbic acid, was proposed by Wright, Lilienfeld and MacLenathen [4a]; they observed that at least 500 mg. was normally excreted in the first twenty-four hours, 75 per cent or more of it during the first five hours. Tests using smaller doses (for example, 100 mg.) are subject to the criticism that moderate changes in the immediately previous vitamin C intake or metabolism may produce proportionately greater changes in the results without indicating the true saturation state. It has been stated that *all* vitamin C in the blood above a certain level spills over into the urine That this is not true is demonstrated by the fact that as little as 36 mg. has been collected after a 1,000 mg. test dose. In most instances the five hour test has been highly satisfactory, but it was first observed in this laboratory [5] that a delay in the excretion of vitamin C occurred in some patients with impairment of renal function. Sendroy and Miller [6] have recently presented similar observations. Thus, erroneous low values may be observed when single urine specimens, obtained three, five, six or eight hours after any test dose of whatever size, are used as criteria of the state of vitamin C nutrition. As would be expected, the levels of vitamin C in the blood under such conditions are found to remain high for longer periods than are normal after the ingestion of the vitamin. Hence, determinations on the blood may give false impressions as to the degree of saturation. In the present investigation the vitamin C content of urine and blood plasma was studied during a twenty-four hour period following an intravenous test dose of 1 Gm. of ascorbic acid. Subjects with and without evidence of renal insufficiency were studied in an effort to evaluate the error due to variations of renal function.

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4. (*a*) Wright, I. S.; Lilienfeld, A., and MacLenathen, E.: Determination of Vitamin C Saturation: A Five Hour Test After an Intravenous Test Dose, Arch. Int. Med. **60**:264 (Aug.) 1937. (*b*) Hawley, E. E., and Stephan, D. J.: Rate of Urinary Excretion of Test Doses of Ascorbic Acid, Proc. Soc. Exper. Biol. & Med. **34**:854, 1936. (*c*) Ralli, E. P.; Friedman, G. J., and Kaslow, M.: An Excretory Test for Vitamin C Deficiency and Subnutrition, Proc. Soc. Exper. Biol. & Med. **36**:52, 1937. (*d*) Finkle, P.: Vitamin C Saturation Levels in the Body in Normal Subjects and in Various Pathological Conditions, J. Clin. Investigation **16**:587, 1937. (*e*) Faulkner, J. M., and Taylor, F. H. L.: Observations on the Renal Threshold for Ascorbic Acid in Urine, ibid. **17**:69, 1938.

5. (*a*) Wright, I. S., and MacLenathen, E.: Vitamin C Saturation—Kidney Retention After Intravenous Test Dose of Ascorbic Acid, Proc. Soc. Exper. Biol. & Med. **38**:55, 1938. (*b*) Wright, I. S.: Cevitamic Acid (Ascorbic Acid; Crystalline Vitamin C): A Critical Analysis of Its Use in Clinical Medicine, Ann. Int. Med. **12**:516, 1938.

6. Sendroy, J., Jr., and Miller, B. J.: Renal Function as a Factor in the Urinary Excretion of Ascorbic Acid, J. Clin. Investigation **18**:135, 1939.

METHOD

Each subject was placed on a diet containing a minimum of vitamin C (less than 15 mg. daily) for at least twelve hours preceding the test and for the twenty-four hours after the administration of the test dose. At 9 o'clock on the morning of the test the patient voided, 6 cc. of blood was drawn for plasma analysis and 1 Gm. of ascorbic acid, dissolved in 10 cc. of physiologic solution of sodium chloride, was injected intravenously. Complete specimens of urine were obtained exactly one and one-half, three and five hours after the injection, and were titrated immediately. The remaining (nineteen hour) specimen was collected in tightly stoppered dark brown bottles, which contained sufficient glacial acetic acid to bring the p_H to 3, and kept at ice box temperature. This specimen was titrated immediately after the last micturition. For a number of the patients with normal vitamin C excretion and for all the patients with delayed excretion, the specimen obtained on the twenty-fourth hour was collected and titrated apart from the rest of the nineteen hour specimen; blood was obtained from these patients at periods corresponding with the urine collections, and the plasma was analyzed for vitamin C.

The vitamin C in the urine was determined by a modification of Tillman's 2, 6-dichlorophenolindophenol method [7] and in the plasma by the sodium tungstate precipitation method of Farmer and Abt.[8] (Duplicate plasma determinations using the metaphosphoric acid technic of Farmer and Abt [9] gave values that agreed within 0.04 mg. per hundred cubic centimeters.) In every instance the plasma analysis was done within thirty minutes after venipuncture, and suitable blanks were used in all titrations. Potassium cyanide was not used as a preservative, since previous studies in our own and other laboratories [10] have shown that it reduces the dye and produces erroneous values.

RESULTS

In normal saturated subjects the vitamin C level in the plasma reached a high peak about two minutes after the injection (chart 1); it fell rapidly during the first hour and one-half and then gradually returned to a point slightly above the control level at the end of twenty-four hours (chart 2). The rate of urinary excretion of vitamin C

7. Tillmans, J.; Hirsch, P., and Jackisch, J.: Das Reduktionsvermögen pflanzlicher Lebensmittel und seine Beziehung zum Vitamin C: Der Gehalt der verschiedenen Obst- und Gemüsearten an reduzierendem Stoff, Ztschr. f. Untersuch. d. Lebensmitt. **63**:241, 1932.

8. Farmer, C. J., and Abt, A.: Ascorbic Acid Content of the Blood, Proc. Soc. Exper. Biol. & Med. **32**:1625, 1935.

9. Farmer, C. J., and Abt, A.: Determination of Reduced Ascorbic Acid in Small Amounts of Blood, Proc. Soc. Exper. Biol. & Med. **34**:146, 1936.

10. (*a*) Wright, I. S., and MacLenathen, E.: Potassium Cyanide as an Agent Inhibiting the Oxidation of Vitamin C in Vitro, J. Lab. & Clin. Med. **24**:808, 1939. (*b*) Friedman, G. J.; Rubin, S. H., and Kees, W.: Effect of Addition of KCN to Whole Blood on Indophenol-Reducing Power of Plasma, Proc. Soc. Exper. Biol. & Med. **38**:358, 1938. (*c*) Farmer, C., and Abt, A.: Invalidation of Plasma Ascorbic Acid Values by Use of Potassium Cyanide, ibid. **38**:399, 1938. (*d*) Cushman, M., and Butler, A. M.: Use of Cyanide in the Determination of Ascorbic Acid, ibid. **39**:534, 1938.

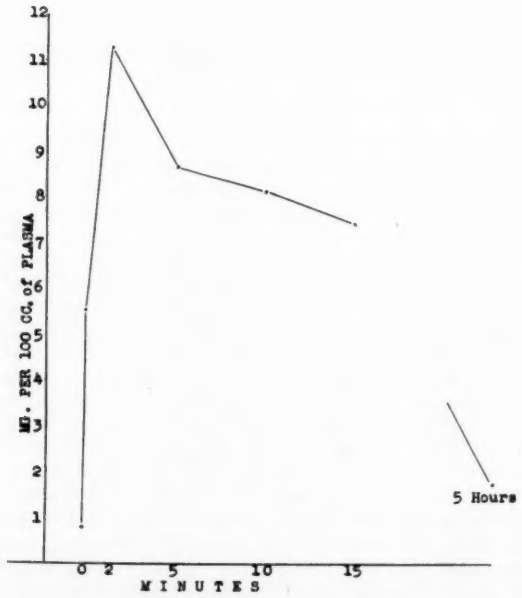

Chart 1.—Vitamin C curve for plasma of a normal subject after intravenous injection of 1 Gm. of ascorbic acid. The five hour output in the urine was 549 mg.

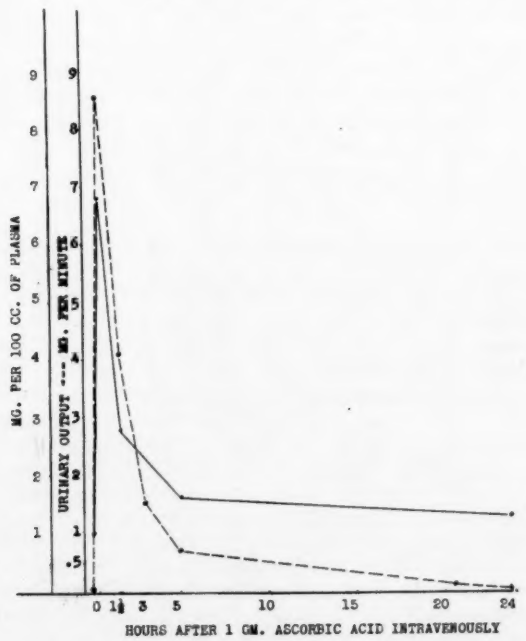

Chart 2.—Typical curves for vitamin C in the urine and plasma of a normal subject; urine, o - - - o; plasma, ●——●. The total excretion in one and one-half hours was 432.9 mg.; in five hours, 661.1 mg.; in twenty-four hours, 788.2 mg.

showed a definite relation to the level in the plasma; it was highest during the first fifteen minutes and remained relatively high during the first hour and one-half, although the fall was rapid until the fifth hour. By this time 75 per cent or more of the total twenty-four hour output had been excreted. The excretion rate had returned to slightly above the control level at the end of twenty-four hours.

In patients with impaired excretion of vitamin C and normal saturation, urinary excretion of vitamin C was slow when compared with the concentration in the plasma. For both urine and plasma, the return

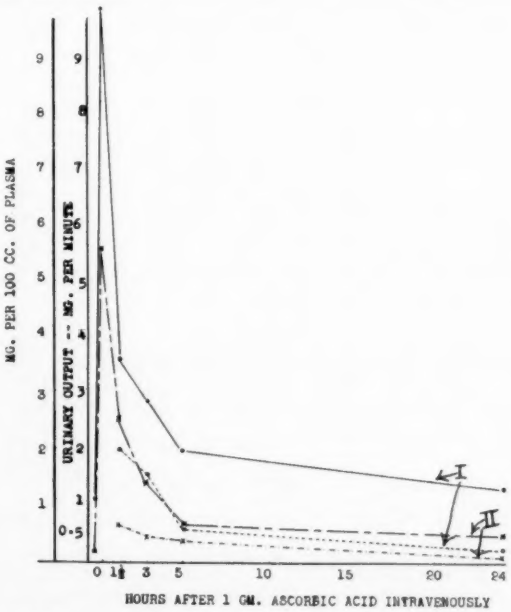

Chart 3.—Vitamin C in the urine and plasma of patients with delayed urinary excretion of the vitamin. Patient I had normal, and patient II had deficient, vitamin C nutrition: urine, I, o-----o; II, x-.-.-.x; plasma I, •——•; II, x— - — - x. The total excretion of vitamin C, in milligrams, was as follows:

	I	II
After one and one-half hours	178.2	53.5
After five hours	380.1	143.6
After twenty-four hours	602.4	237.1

toward control levels was delayed for varying periods. In patients with impaired excretion, but in an unsaturated state of vitamin C nutrition, the vitamin C content of the plasma dropped normally although that of the urine showed evidence of impaired excretion (chart 3). The urine

appeared to give more reliable evidence of the renal function in regard to vitamin C than the plasma.

The significant data for 8 patients with evidence of impaired vitamin C excretion are presented in Table 1, together with the results of other laboratory studies pertaining to renal function. The impairments of excretion in patients J. K., J. M. and F. M. were discovered in the course of routine studies and there was no other evidence to suggest renal insufficiency; these patients were all men over 65 years of age with

TABLE 1.—*Results for Patients with Impaired Vitamin C Excretion*

			Vitamin C				Blood			Urine		
Patient	Age	Diagnosis	Control Plasma, Mg. per 100 Cc.	5 Hour Urine, Mg.*	24 Hour Urine, Mg.*	5/24 Hr. Excr., %†	Nonprotein Nitrogen	Urea Nitrogen	Urea Clearance, % of Normal	Specific Gravity	Protein	Rbc./H.P.F.
JK	80	Arteriosclerosis.....	0.95	380	602	63	29	14	104	1.020	0	0
JM	69	Arteriosclerosis.....	1.03	506	845‡	60	40	13	76	1.012	0	0
FM	67	Arteriosclerosis.....	0.16	143	237	60	24	13	135	1.020	Tr.	1
MB	45	Malignant hypertension.	0.31	179	271	66	29	16	62	1.008§ 1.012	2+	13
SB	25	Malignant hypertension.	0.59	139	257	54	55	28	29	1.006§ 1.018	3+	3
MF	28	Chr. glomerulonephritis.	0.49	240	444	54	54	43	31	1.009§ 1.015	2+	1
JP	42	Chr. pyelonephritis (in uremia)	0.34	30	83	35	125	80	11	1.004§ 1.010	1+	1
MT	17	Malignant hypertension (in uremia)	1.50	78	151‡	52	75	..	..	.....	1+	..

* After 1 Gm. ascorbic acid intravenously.
† Percentage of the 24 hour output excreted during the first 5 hours.
‡ Computed from data of 5 hour test.
§ Maximum variations during Mosenthal 2 hour test.

obliterative peripheral arteriosclerosis. Patients M. B., S. B. and M. F. all had other clinical and laboratory evidence of diminished renal function. (The curve of ascorbic acid excretion of patient S. B. is compared with that of a patient with normal renal function and a similar vitamin C deficiency in chart 4.) In all of these patients except J. P. and M. T., who were in terminal uremia when studied, the twenty-four hour plasma and urine vitamin C levels had returned to slightly above control values. We have interpreted this as evidence that the twenty-four hour excretion was a satisfactory index of saturation except in these 2 cases of far advanced renal insufficiency. Gross errors, however, would have resulted in every case if the three or five hour output had been used as an index of saturation. The data for patient J. K. will illustrate the magnitude

of this error: The five hour output, of 380 mg., gave evidence of a deficiency, whereas the twenty-four hour output, of 602 mg., was entirely normal.

The results of twenty-four hour excretion studies of 29 subjects with a wide range of saturation levels and with various degrees of renal efficiency are presented in table 2.

The proportion of the twenty-four hour output of vitamin C excreted during the first five hours after the test dose varied from 54 to 99 per cent. These variations appeared to depend, to some extent, on the state of saturation, but a very important factor was the renal function in relation to vitamin C. The curves for vitamin C in the urine of subjects 11, 16,

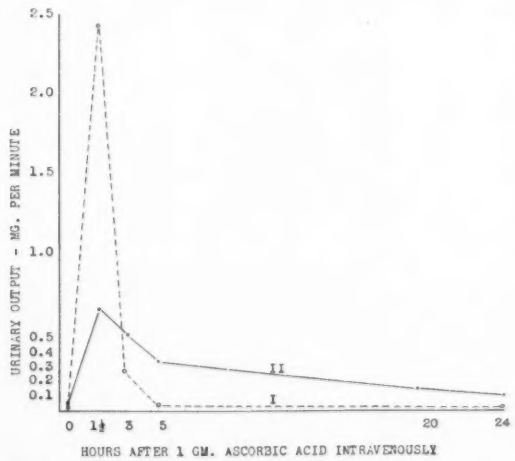

Chart 4.—Comparison of excretion of vitamin C following test dose by (I) a patient with normal renal function and (II) a patient with impaired renal function, both patients having vitamin C deficiency. The total excretion of the vitamin, in milligrams, was as follows:

	I	II
After one and one-half hours	222	58
After five hours	247	138
After twenty-four hours	253	256

The urea clearance in patient I was 135 per cent; in patient II, 29 per cent.

20, 23 and 26, indicated delayed excretion; the proportion of the twenty-four hour output excreted in the first five hours ranged from 54 to 66 per cent. The curves for subjects 12 and 7 showed moderately impaired excretion; although there was no clear laboratory evidence of impaired renal function, both subjects were aged men with marked peripheral arteriosclerosis. The vitamin C excretion for the remaining 22 subjects

was interpreted as being within normal limits, although the five hour output varied from 77 to 99 per cent of the twenty-four hour output. The five hour output was observed to become proportionately less in relation to the twenty-four hour output as the state of saturation improved. This observation was confirmed by tests done on patients

TABLE 2.—*Results of Twenty-Four Hour Vitamin C Excretion Tests After Intravenous Injection of 1 Gm. of Ascorbic Acid*

			Actual Urinary Output of Vitamin C						
Subject	Vitamin C in Diet	Control Plasma, Mg. per 100 Cc.	1½ Hr., Mg.	5 Hr., Mg.	24 Hr., Mg.	1½/5 Hr. Excr., %*	5/24 Hr. Excr., %†	Predicted 24 Hr. Output,‡ Mg.	Percentage of Error§
1	Exc.	0.98	432.9	661.1	788.2	65.4	83.9	779.9	1.04
2	Exc.	1.17	423.0	689.4	784.8	61.3	87.8	842.0	7.26
3	Exc.	....	359.2	603.2	757.0	59.5	79.6	747.8	1.21
4	Exc.	1.32	414.0	637.0	737.6	65.0	86.3	754.2	2.25
5	Exc.	1.41	377.8	618.8	732.3	61.1	84.5	757.3	3.27
6	Good	0.78	352.0	562.9	716.8	62.5	78.5	679.6	5.18
7	Good	0.95	267.1	483.4	674.8	55.2	71.6	626.8	7.10
8	Good	0.58	327.4	510.8	633.4	64.1	80.6	609.0	3.85
9	Good	0.91	313.6	522.3	624.5	60.4	83.6	644.6	3.21
10	Good	0.41	304.0	479.5	620.5	63.4	77.3	574.8	7.37
11	Good	0.95	178.2	380.1	602.4	46.8	63.1	555.6	7.76
12	Good	0.57	218.5	430.1	585.2	50.8	73.7	590.4	0.89
13	Fair	0.50	341.9	479.5	526.8	71.3	91.0	544.1	3.28
14	Fair	0.61	265.5	418.7	497.8	63.4	84.0	502.5	0.94
15	Good	0.79	266.2	418.2	481.1	63.6	86.9	500.3	4.44
			Low Normal Level						
16	Fair	0.49	87.7	239.8	443.7	36.7	54.1	458.9	3.42
17	Fair	0.22	290.4	358.2	374.0	81.0	95.7	386.3	3.28
18	Poor	0.17	286.0	311.1	315.9	91.9	98.4	321.9	1.90
19	Fair	0.30	234.4	269.4	283.4	87.0	95.1	283.7	0.05
20	Fair	0.31	75.5	179.1	271.1	42.1	66.1	289.0	6.62
21	Poor	0.26	237.4	262.5	268.7	90.4	97.6	273.0	1.60
22	Fair	0.26	245.4	263.3	265.3	93.4	99.2	271.3	2.26
23	Fair	0.59	58.3	138.5	256.4	42.1	54.3	223.9	12.67‖
24	Fair	0.33	221.9	247.0	252.3	89.9	97.9	257.4	2.02
25	Poor	0.13	216.6	240.0	246.4	90.3	97.7	249.8	1.33
26	Poor	0.16	53.5	143.6	237.1	37.2	60.5	268.3	13.20‖
27	Poor	0.17	194.7	211.6	221.7	92.0	95.4	218.8	1.31
28	Poor	0.09	88.3	103.3	108.7	85.6	95.0	109.4	0.65
29	Poor	0.18	97.4	97.6	97.9	99.8	99.8	98.6	0.71
								Mean	3.12 + 2.3

* Percentage of the 5 hour output excreted the first 1½ hours.
† Percentage of the 24 hour output excreted the first 5 hours.
‡ Predicted 24 hour output according to the formula in the text.
§ Percentage of error of predicted 24 hour output when compared with actual 24 hour output.
‖ Omitted from calculation of mean due to large relative deviation.

both before and after saturation; typical results of such a study may be seen in chart 5. In our experience the factor of saturation does not account for five hour excretion percentages of less than 75.

A careful study of the accumulated data revealed a definite correlation between (1) the percentage of the five hour output excreted during the first one and one-half hours and (2) the percentage of the twenty-four hour output excreted during the first five hours. Accordingly, this correlation was analyzed as follows: A graph, employing these variables,

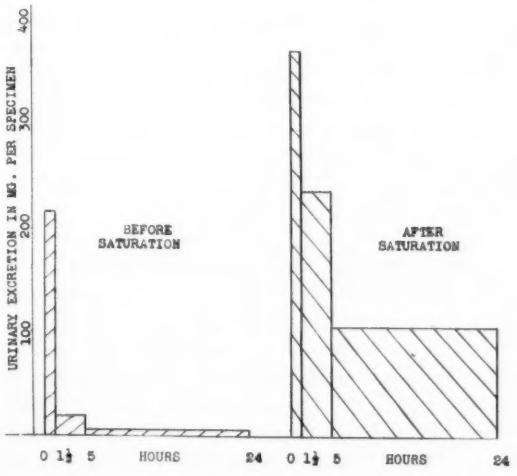

Chart 5.—Effect of previous saturation on the twenty-four hour excretion of vitamin C after the intravenous injection of 1 Gm. of ascorbic acid. The patient received 4,600 mg. of ascorbic acid orally during the five days between tests. Before saturation, 247 mg. was excreted in twenty-four hours and 240 mg. (97 per cent) in the first five hours. After saturation, 732 mg. was excreted in twenty-four hours and 618 mg. (84 per cent) in the first five hours.

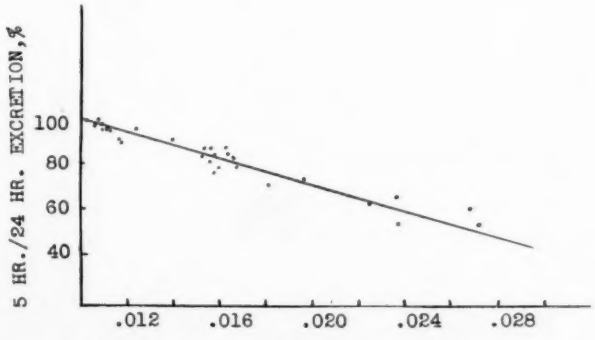

Chart 6.—The percentage of the twenty-four output of vitamin C excreted during the first five hours after the test dose is plotted against the reciprocal of the percentage of the five hour output excreted in the first one and one-half hours. The line is drawn from the formula given in the text; the dots represent the experimental values.

was plotted from the tabulated data, and the shape of the resulting curve indicated an equation of the form $y = a + b/x$, with y representing the percentage of the twenty-four hour output excreted in five hours and x representing the percentage of the five hour output excreted in one and one-half hours. We set $x' = 1/x$ and calculated the values of x'. Plotting points x' and y, we found that they lay nearly on a straight line (chart 6). Values for a and b were obtained from the data by the method of averages. By simple substitution the following working formula was then developed:

$$C = \frac{ab}{1.26\,a - 0.27\,b}$$

In this formula, C represents the amount of vitamin C (in milligrams) excreted in twenty-four hours; a, the amount excreted in one and one-half hours, and b, the amount excreted in five hours.

With this formula, the data for one and one-half and five hour urine specimens were sufficient to predict the actual twenty-four hour output with a mean error of 3.12 ± 2.3 per cent and a maximum error of 13 per cent. This degree of error seemed relatively insignificant when compared with the constant and possible errors of previously described urinary excretion tests.

Accordingly, we suggest the following modified technic for the original [48] five hour vitamin C saturation test:

Have the patient omit breakfast on the morning of the test. Immediately after the patient has voided and discarded the preliminary urine, inject intravenously 1 Gm. of ascorbic acid dissolved in 10 cc. of physiologic solution of sodium chloride. Collect urine specimen 1 exactly one and one-half hours after the injection and specimen 2 exactly five hours after the injection. Titration preferably should be done immediately after each collection; but, if necessary, the first specimen may be preserved as outlined previously and titrated at the end of the test.

By means of the values obtained for specimen 1 (a) and the sum of those for specimens 1 and 2 (b), the predicted twenty-four hour excretion, C, may be calculated according to the formula $C = \frac{ab}{1.26\,a - 0.27\,b}$. The value thus calculated may be termed the *saturation index*.

COMMENT

This modification has retained all the advantages of the original five hour vitamin C saturation test [48] and has compensated for the error due to variations in renal function. The only patients so far found to be unsuitable for this test were in advanced uremia. Such patients can be readily recognized and do not present problems primarily of vitamin C nutrition. Hyperavitaminosis C may be easily produced in such patients if large repeated doses are given. Parallel studies of the content in the plasma and the urine, followed by daily analyses of the plasma during vitamin C therapy, have clarified the interpretation of these rare exceptions.

These studies also appeared to confirm the observations of Van Eekelen,[11] Lund,[12] Faulkner and Taylor [10] and Ralli, Friedman and Rubin [13] that a definite augmentation in the rate of vitamin C excretion occurred when the level in the plasma exceeded 1.2 to 1.4 mg. per hundred cubic centimeters. As the values fell below this "threshold" the rate of excretion gradually decreased, although some vitamin C continued to be excreted even when the level in the plasma was very low.

Since a definite delay of vitamin C excretion was observed in several aged persons with no other evidence of renal insufficiency, the question arose whether some renal impairment existed which was not determined by the usual tests of renal function. More detailed studies and prolonged observations of such patients will be necessary for the exact evaluation of this question. At the present time, we should interpret the data as indicating impaired vitamin C excretion when the vitamin C output during the first one and one-half hours after the test dose is less than half the total five hour output. Such delayed excretion would appear to be more significant in unsaturated than in saturated persons. The use of other well established renal function tests seems indicated for such persons.

SUMMARY

A modified five hour vitamin C saturation test which compensates for the error due to variations in renal function is proposed.

Twenty-four hour studies of the urinary excretion and plasma concentration of vitamin C after an intravenous test dose of 1 Gm. of ascorbic acid are reported for patients with a wide range of saturation levels and with various degrees of renal insufficiency.

Except for patients in the uremic state the twenty-four hour excretion appears to give a satisfactory index of the state of vitamin C nutrition. The excretion during shorter test periods gives false low values for patients with retarded vitamin C excretion. Patients with impaired renal excretion of vitamin C may give no other evidence of renal insufficiency.

A correlation exists between (1) the percentage of the five hour output excreted during the first one and one-half hours after the

11. Van Eekelen, M.: On the Amount of Ascorbic Acid in Blood and Urine: The Daily Human Requirements for Ascorbic Acid, Biochem. J. **30**:2291, 1936.

12. Lund, H.: Eine quantitative und spezifische Methode zur Ascorbinsäuretitration im Harn und zur Bestimmung des Schwellenwertes, Klin. Wchnschr. **16**:1085, 1937.

13. Ralli, E. P.; Friedman, G. J., and Rubin, S. H.: The Mechanism of Vitamin C Excretion in Man Studied by Simultaneous Vitamin C and Inulin Clearances, J. Clin. Investigation **17**:765, 1938.

test dose and (2) the percentage of the twenty-four hour output excreted during the first five hours. In view of this, a formula is presented by which the actual twenty-four hour output may be satisfactorily predicted through the use of data on urine specimens obtained one and one-half and five hours after the test dose.

The proposed test, in our experience, gives a more reliable estimation of the actual state of vitamin C saturation than any other method available at this time.

In addition, an estimation of the renal function for vitamin C may be obtained through the analysis of data from this test.

FEVER IN CONGESTIVE HEART FAILURE

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AND
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It is well known that fever often occurs in patients with congestive heart failure. During the early use of the clinical thermometer Wunderlich [1] noted this finding, but he also said that subnormal temperatures were by no means uncommon.

In reviewing the medical literature it is surprising to find so little has been said either about fever in relation to congestive heart failure or concerning the frequency with which complications occur in patients suffering from that disease.

Harrison's [2] opinion, as expressed in his book entitled "Failure of the Circulation," is as follows:

> Fever in some degree occurs in a large proportion of patients with congestive heart failure. A slight increase in temperature may possibly be dependent on the increase in the metabolic rate which many patients exhibit, but fever of more considerable magnitude usually signifies infection, infarction, or thrombus formation. More commonly fever is to be ascribed to pulmonary infection.

Cohn and Steele [3] reviewed 172 cases in which symptoms or signs of heart failure were presented. In 153 of these cases there were, on two or more occasions, elevations of rectal temperature to at least 100 F. In 49 cases the occurrence of fever was without satisfactory explanation, and after completing their study the authors came to the conclusion that heart failure alone could cause fever, by interference with heat loss. In only 9 cases of their series, however, were postmortem examinations made.

PRESENT STUDY

We have reviewed the cases of 200 patients with congestive heart failure who were admitted to the Massachusetts General Hospital from 1933 to 1938. These cases include all types of cardiac disease. In every

From the Medical Clinic of the Massachusetts General Hospital.

Read at the Annual Meeting of the American Heart Association, St. Louis, May 12, 1939.

1. Wunderlich, C. R. A.: On the Temperature in Diseases: A Manual of Medical Thermometry, London, New Sydenham Society, 1871, pp. 430 and 431.

2. Harrison, T. R.: Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1936, p. 264.

3. Cohn, A. E., and Steele, J. M.: Unexplained Fever in Heart Failure, J. Clin. Investigation **13**:853, 1934.

instance rectal temperature readings were taken.[4] Postmortem examinations were made of 50 of the 81 patients who died in the hospital. We have classified the grades of fever and of heart failure as follows:

Type and Grade of Heart Failure.[5]—(1) Left ventricular failure alone—dyspnea, with or (usually) without moist rales at the bases of the lungs, accentuation of the second pulmonary heart sound, diastolic gallop at the cardiac apex and pulsus alternans; (2) slight to moderate right ventricular failure—enlargement of the liver and slight to moderate dependent edema; (3) marked right ventricular failure—anasarca.

Grade of Fever.—(0) no fever; (1) slight fever—not over 1 degree (100.4 F., rectal); (2) moderate fever—1 to 2.5 degrees; (3) over 2.5 degrees.

TABLE 1.—*Entire Group (200 Patients, Including 50 Examined Post Mortem)*

Heart Failure		Fever				Sex		Age				Cause				
Grade	Number	None	1 Degree	2½ Degrees	Over 2½ Degrees	Male	Female	0 to 20	20 to 40	40 to 60	60 to 80	Rheumatic	Hypert.	Coronary	Hyp. & Cor.	Miscellaneous
1 Slight	16 8%	0	4	4	8	12	4	2	3	4	7	4	6	2	2	2
2 Moderate	71 35.5%	3	14	19	35	38	33	13	19	26	13	37	6	11	3	14
3 Marked	113 56.5%	1	22	42	48	77	36	7	14	48	44	39	23	7	17	27
Total	200	4	40	65	91	127	73	22	36	78	64	80	35	20	22	43
Percentage...		2	20	32.5	45.5	63.5	36.5	11	18	39	32	40		38.5		21.5

Entire Series.—Of the 200 patients studied (table 1), 127 were males and 73 were females; 16 had left ventricular failure alone, 71 slight to moderate right ventricular failure, and 113, or over half, marked right ventricular failure. Twenty-two patients were below 20 years of age;

4. Oral temperatures are notoriously unreliable as an indication of internal body temperature in the presence of dyspnea, which so often necessitates mouth breathing with resultant cooling and drying of the mucous membranes of the mouth.

5. Left ventricular failure alone, usually based on the symptom of dyspnea in cases with cardiac enlargement secondary to systemic hypertension, aortic valvular disease or large myocardial infarcts, is graded as 1 with reference to extent of stasis, moderate or marked pulmonary vascular engorgement occurring only transiently in attacks of paroxysmal dyspnea in a few of the cases; right ventricular failure, as a rule secondary either to failure of the left ventricle or to disease of the mitral valve, is graded as 2 and 3, respectively, because of the obvious and chronic generalized stasis in the systemic circulation.

36 were from 20 to 40; 78 were from 40 to 60, and 64 were from 60 to 80. As to the cause, rheumatic heart disease heads the list, with a total of 80 patients (40 per cent); 77 other patients had hypertensive, hypertensive and coronary or coronary heart disease, while the remaining 43 had one of the various other types of disease of the heart. Only 4 patients of the whole series of 200 were entirely free from fever during their stay in the hospital, and yet 3 of these 4 patients had moderate failure and 1 had marked failure. It is interesting to note that 48, or less than 50 per cent, of the 113 patients with marked failure had fever of over 2.5 degrees, whereas 8 of the 16, or exactly 50 per cent, of the group with slight failure had fever of over 2.5 degrees.

TABLE 2.—*Cases in Which Autopsy Was Performed*

Heart Failure		Fever				Complications							
Grade	Number	None	1 Degree	2½ Degrees	Over 2½ Degrees	Pulmonary Infarction	Bronchopneumonia	Other Respiratory Infections	Active Rheumatic Infection	Acute Coronary Thrombosis	Other Complications	Questionable Number Without Complications	
1 Slight	5 10%	0	0	1	4	3	2	0	0	1	.....	0	0
2 Moderate	18 36%	0	1	1	16	6	8	1	3	4	Cerebral hemorrhage, subacute bacterial endocarditis, parotitis, cerebral embolism	0	0
3 Marked	27 54%	0	1	12	14	15	10	2	5	3	Pyelonephritis, cerebral thrombosis, infarction of spleen, infarction of pancreas, subacute bacterial endocarditis and rheumatic arthritis, septicemia	0	0
Total....	50	0	2	14	34	24	20	3	8	8	11	0	0
Percentage.....		4	28	68	48	40	6	16	16	22			

Fatal Termination; Autopsy Performed.—Table 2 presents data for the 50 cases in which autopsy was performed. There were 5 patients with grade 1 heart failure in this group, 1 of whom had 2.5 degrees of fever and others over 2.5 degrees. All 5 patients had complications: Three had pulmonary infarction; 2 had bronchopneumonia, and 1 had acute coronary thrombosis.

In the same group of 50 patients there were 18 with grade 2 heart failure: One had 1 degree of fever, 1 up to 2.5 degrees and the remaining 16 over 2.5 degrees. All 18 had complications, several more than one. Six had pulmonary infarction, 8 bronchopneumonia, 1 pneumonitis, 3 active rheumatic infection, 4 acute coronary thrombosis and 4 other complications, as listed in table 2.

Twenty-seven of the 50 patients had grade 3, or marked, heart failure: One had up to 1 degree F. of fever; 12, up to 2.5 degrees, and 14, over 2.5 degrees. All 27 had complications: Fifteen had pulmonary infarction, 10 bronchopneumonia, 2 pneumonitis, 5 acute rheumatic infection, 3 acute coronary thrombosis and 7 one of the other complications noted in the table.

In this group of 50 patients there were none without fever and, likewise, none without at least one complication that could be responsible for fever. In several instances there was more than one complication that might have caused the fever.

TABLE 3.—*Fatal Cases in Which No Autopsy Was Performed*

Heart Failure		Fever				Complications							
Grade	Number	None	1 Degree	2½ Degrees	Over 2½ Degrees	Pulmonary Infarction	Bronchopneumonia	Other Respiratory Infections	Active Rheumatic Infection	Acute Coronary Thrombosis	Other Complications	Questionable Number Without Complications	
1 Slight	1 3.2%	0	0	0	1	1	0	0	0	0	.....	0	0
2 Moderate	14 45%	0	1	2	11	6	3	0	5	0	Cerebral embolism	1	0
3 Marked	16 51.6%	0	2	4	10	2	2	1	4	2	Embolism in leg, acute polyserositis, cerebral hemorrhage	3	0
Total....	31	0	3	6	22	9	5	1	9	2	4	4	0
Percentage.....			9.6	19.3	70.9	29	16.1	3.2	29	6.4	12.9	12.9	

Thus, of these 50 patients, a total of 48 per cent had pulmonary infarction, 40 per cent bronchopneumonia, 16 per cent acute rheumatic infection and 16 per cent acute coronary thrombosis. There was no patient with congestive heart failure alone and no patient without fever.

Fatal Termination; No Autopsy.—Table 3 presents data for the 31 patients in whose cases death occurred and autopsy was not performed. In this group 1 patient had grade 1 heart failure, 14 grade 2 failure and 16 grade 3, or marked failure. Twenty-seven of the 31 patients had a known complication that could account for fever, and the remaining 4 patients had questionable complications—that is, complications were suspected but not definitely diagnosed. In this entire group of 31 patients, 29 per cent had pulmonary infarction, 16.1 per cent bronchopneumonia, 29 per cent active rheumatic infection and 6.4 per cent acute coronary thrombosis.

Surviving Group.—Table 4 presents data for the surviving group—that is, the patients that were discharged alive from the hospital. In this group of 119 patients, 10 had grade 1 heart failure, 38 grade 2 failure and 71 grade 3, or marked, failure. The incidence of fever in relation to heart failure was approximately the same as it was in the previous groups, but complications were diagnosed less frequently: Fourteen per cent of the patients had pulmonary infarction, 7.5 per cent bronchopneumonia and 17.6 per cent active rheumatic infection. The diagnosis of acute coronary thrombosis was not made. In 28 patients a complication was suspected, but in 26 others it was neither diagnosed nor suspected. Of the latter 26 patients, 4 had no fever and 16 had fever

TABLE 4.—*Surviving Group*

Heart Failure		Fever				Complications							
Grade	Number	None	1 Degree	2½ Degrees	Over 2½ Degrees	Pulmonary Infarction	Bronchopneumonia	Other Respiratory Infections	Active Rheumatic Infection	Acute Coronary Thrombosis	Other Complications	Questionable	Number Without Evident or Questionable Complications
1 Slight	10 8.4%	0	4	3	3	3	2	0	2	0	.....	1	2
2 Moderate	38 31.9%	3	12	15	8	4	1	6	12	0	2, infection of urinary tract; 2, streptococcic sore throat	6	6
3 Marked	71 59.6%	1	19	27	24	10	6	4	7	0	Cerebral infarction, renal infarction, renal infection, 2 cystitis	21	18
Total....	119	4	35	45	35	17	9	10	21	0	9	28	26
Percentage.....		3.3	29.4	37.8	29.4	14.2	7.5	8.4	17.6	0	7.5	23.5	21.8

of only 1 degree (F.). Perhaps if a more diligent effort had been made to determine the cause of obscure fever in these cases, a greater number of complications might have been found.

COMMENT

Cohn and Steele [3] observed that in their series of cases fever and heart failure disappeared simultaneously. We have not found this to be true in our series; instead, it is apparent that in many instances the elevation in temperature was related to the complication rather than to the heart failure, occurring as it did with or after the development of a complication. For example, 1 patient, a 24 year old man, entered the hospital in November 1935; the diagnosis included rheumatic heart disease, mitral stenosis and regurgitation, auricular fibrillation and marked heart failure. He remained in the hospital three weeks, during

which time he was fever free and there was no evidence of active infection. He was readmitted on Jan. 17, 1936, with marked heart failure, as before, and remained in the hospital until March; during this time leukocytosis developed, and he had other evidence of active rheumatic infection. His temperature became elevated to 101.4 F. (rectal).

In the cases of some of our patients who were admitted with congestive heart failure and a complication such as bronchopneumonia or pulmonary infarction, the fever, heart failure and complication all subsided simultaneously. In a number of these instances it is certain that the complication was the chief factor responsible for the heart failure.

It has been asked whether complications may not occur without fever. No doubt this is occasionally true, as shown by one of our patients, who had two hospital visits. A girl 13 years of age was admitted to the hospital Oct. 25, 1935. The diagnosis was rheumatic heart disease with mitral stenosis and regurgitation, active rheumatic infection and marked congestive heart failure. She had leukocytosis throughout her nine day stay in the hospital, the highest count being 20,000, but at no time did her rectal temperature go above 99.4 F. The patient was readmitted Aug. 24, 1936, with the same diagnosis, and died Nov. 8, 1936. During this period her rectal temperature remained below 99.4 F. for the most part; on one occasion it was elevated to 101 F.

Our experience in this case, and in other cases of infectious disease not in the present series demonstrates the well recognized facts (1) that sometimes infections occur without fever, (2) that for certain persons a high "normal" temperature really means fever and (3) that, conversely, half a degree or so of "fever" may be normal for certain persons when excited or very restless. All of these considerations must be taken into account in each case of congestive heart failure as much as in a case of any other disease.

No doubt small infarctions of the heart or lung may occur without causing fever, as is true of active rheumatic fever, or the fever in these conditions may be of short duration or unusual periodicity so that it is missed, unless the temperature is taken often.

Only 1 case of congestive heart failure precipitated by paroxysmal tachycardia was included in our study. A small boy, 4 years of age, had two admissions to the hospital. At the time of the first hospitalization, from May 13 to June 22, 1933, the diagnosis was paroxysmal tachycardia and acute tonsillitis. The temperature was elevated during the first part of the stay in the hospital, as a result of the tonsillitis, the highest reading being 102 F. (rectal). Mild congestive failure developed after prolonged paroxysmal tachycardia. The second admission was on July 20, 1933, and the patient died seven days later, after a cerebral infarction,

which occurred early on the day of death. Postmortem observations were as follows: cardiac hypertrophy; mural thrombus, left ventricular wall; cerebral embolism and infarction; congenital bicuspid aortic valve; endocarditis; diffuse thickening of the endocardium; bilateral hydrothorax; hydropericardium, and pulmonary congestion. The rectal temperature at no time was higher than 99.4 F. until the seventh day, before death, when, owing to the cerebral infarction, it was 101.8 F.

Emerson,[6] in discussing pulmonary infarction, noted that patients often show temperatures of 99 to 100 F. daily for a week or two previous to pulmonary infarction—evidence probably of thrombophlebitis. Assuming that this is true, it is possible that a certain number of patients may have concealed thrombophlebitis which would account for fever, without actual development of pulmonary infarction.

The basal metabolic rate in some cases of congestive heart failure is considerably above the normal level. The cause of this elevation is not entirely understood, but it is thought to be due to the increased work of the body as a result of such symptoms as dyspnea and cough; also, the myocardium itself consumes more than its normal amount of oxygen, owing to its increased bulk and inefficiency. In our series, however, the basal metabolic rate was elevated to plus 20 per cent or more in only 3 of the 12 cases of congestive failure in which the rate was determined. In none of the 3 was there thyrotoxicosis, so far as could be determined. No basal metabolic rate was as high as plus 40 per cent, despite the presence of fever in all 12 patients and of complications in most of them. A complication inducing fever is probably more likely than is congestive heart failure itself to raise the basal metabolic rate.

SUMMARY AND CONCLUSIONS

Two hundred cases of congestive heart failure have been reviewed to determine the incidence and cause of fever in this condition.

In 81 of the cases the patients died, and in 50 cases autopsy was performed. At least one complication was found in each of these 50 cases to which might be attributed the fever that had been present. In all of the remaining 31 cases in which autopsy was not performed fever was present, and in 27 of these a complication which could account for fever was found; in the other 4 cases such a complication was suspected but was not proved.

In 119 cases the patients survived; fever was present in all but 4, and in these 4 cases no complications were found. A complication was diagnosed or suspected in 93 of the 119 cases. In 22 cases in which fever

6. Emerson, C. P., in Cecil, R. L.: A Textbook of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1937, p. 866.

was present a complication was neither diagnosed nor suspected; in 16 of these the fever was of only 1 degree (F.) or less.

Thus, although congestive heart failure alone may possibly explain up to 1 degree of fever, there was almost invariably some underlying complication to account in general for fever in the cases of congestive heart failure which we have studied. In order of frequency the four most common complications were: pulmonary infarction, pulmonary infection (especially bronchopneumonia), active rheumatic infection and acute coronary thrombosis.

Fever of any grade in a case of congestive heart failure should be considered as probable evidence of some complicating condition, which not only frequently explains intractability to treatment but also may be the cause of death, which rarely occurs with heart failure alone.

BASAL SECRETION OF DIGESTIVE ENZYMES IN OLD AGE

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AND
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In a previous communication [1] we reported that salivary ptyalin is diminished in the aged. The present study was undertaken to determine the activity under fasting conditions of the enzymes in saliva, in gastric juice and in duodenal juice by several of the newer enzyme methods as well as to compare any further differences in enzyme activity between these various secretions in young and in old persons.

MATERIAL AND METHOD

A total of 61 subjects were tested, 29 of them being between 60 and 96 years of age and the remainder, 32, varying in age from 12 to 60 years. Normal subjects were tested, but most of the members of the older age group showed one or another of the infirmities of old age. Most of the old subjects were residents of a home for the aged. The younger group consisted of suitable clinical patients, interns and graduate students.

The ptyalin content of the saliva was tested by two methods: (*a*) the Wohlgemuth method as described by Hawk and Bergheim; [2] one unit of ptyalin is expressed as the amount required to digest 5 cc. of a 2 per cent starch solution to the achromic point; and (*b*) the method of Ross and Shaw; [3] one unit of amylase is the amount of enzyme which will liberate 5 mg. of maltose under the conditions described in this communication.

For determination of the values for pepsin and trypsin we used the methods of Anson and Mirsky.[4] Pepsin: The activity of the enzyme is determined by comparing its ability to form tyrosine in five minutes with a standard solution containing 0.15 mg. of tyrosine. Trypsin: The tyrosine formed by the enzyme in five minutes is compared with a standard solution containing 0.25 mg. of tyrosine.

From the Departments of Medicine, of Gastrointestinal Research and of Chemistry, Michael Reese Hospital.

1. Meyer, J.; Golden, J. S.; Steiner, N., and Necheles, H.: The Ptyalin Content of Human Saliva in Old Age, Am. J. Physiol. **119**:600, 1937.

2. Hawk, P. R., and Bergheim, O.: Practical Physiological Chemistry, ed. 10, Philadelphia, P. Blakiston's Son & Co., 1931, p. 263.

3. Ross, J. R., and Shaw, M. M.: Determinataion of Pancreatic Amylase, J. Biol. Chem. **104**:131, 1934.

4. Anson, M. L., and Mirsky, A. E.: Determination of Proteases, J. Gen. Physiol. **16**:59, 1932; **17**:151, 1933.

For determination of lipase the method of Cherry and Crandell [5] was used; after an incubation period of twenty-four hours the fatty acids are titrated with one-twentieth normal sodium hydroxide.

All observations were made on fasting subjects, and the samples were put into an ice box immediately after collection. The saliva was collected after rinsing the mouth with water. The gastric and duodenal juices were aspirated by a rubber tube with a double lumen as used by Miller and Abbot.[6] One tube, with a duodenal bucket attached to the tip, went down to the duodenum, and the other had openings approximately 15 cm. above this point for aspiration of the gastric contents. These contents were continuously aspirated by siphonage into the flask which was placed about 30 inches (75 cm.) below the level of the stomach, while the duodenal juice was aspirated by syringe. The first samples were discarded, and only the bile-stained alkaline juice was tested. One hour was generally required to intubate the duodenum. In about 15 per cent of all cases we did not obtain the duodenal juice, because the tube was doubled in the stomach or would not pass into the duodenum.

RESULTS AND COMMENT

The concentration of ptyalin in the saliva of old persons as determined by the Wohlgemuth method is less than one third of the amount present in the saliva of young persons, but by the method of Ross and Shaw the concentration of ptyalin for the older group is about two thirds of that for the control group (chart 1). Olson, Fricke and Kaja [7] assumed the presence of two enzymes in saliva, which are differentiated by their effect on carbohydrates, the amyloclastic action and the maltose-forming effect. The Wohlgemuth iodine reaction shows only the digestion of starch to achroodextrin (amyloclastic action), whereas the other method indicates the amount of maltose formed. This fact may explain the difference in our results as obtained by these two methods. The concentration of sodium chloride in the enzyme systems tested by the two methods may influence the results, but we found that different concentrations of sodium chloride affected the results very little. It is evident that in aged persons salivary amylase is decreased. This confirms our previous studies.

The concentration of pancreatic amylase (chart 2) is subnormal in old age. It is interesting to note that in the age group between 81 and 100 we found values which reached the average level for the younger group. The higher value for pancreatic amylase may be a substitute for the lower value for salivary ptyalin in old age. Our results suggest that completion of the digestion of carbohydrates is not markedly disturbed in the aged.

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5. Cherry, J. S., and Crandell, L. A.: The Specificity of Pancreatic Lipase, Am. J. Physiol. **100**:266, 1932.

6. Miller, J. G., and Abbot, W. O.: Intestinal Intubation: A Practical Technique, Am. J. M. Sc. **187**:595, 1937.

7. Olson, Fricke and Kaja, cited by Oppenheimer, C.: Die Enzyme und ihre Wirkungen, The Hague, W. Junk, 1933.

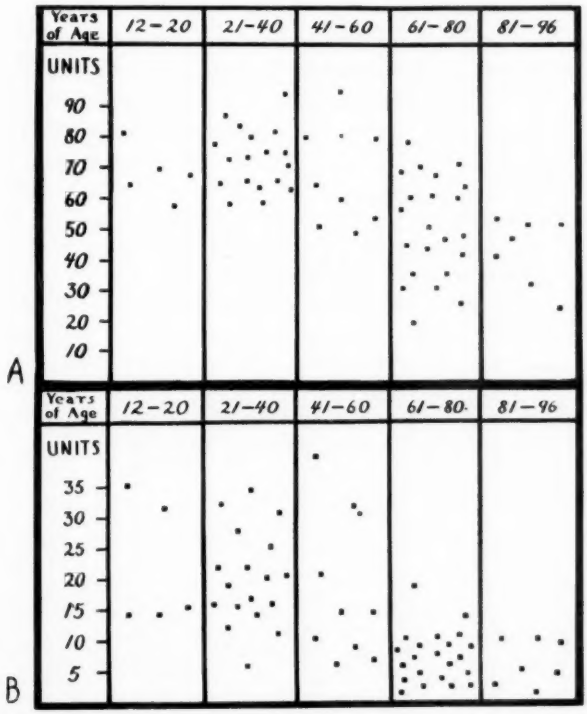

Chart 1.—*A*, salivary ptyalin estimated by the Shaw and Ross method. The enzyme activity falls little in the older age groups, although a downward trend is evident. The reaction is carried to completion, i. e., to the formation of maltose. *B*, salivary ptyalin estimated by the Wohlgemuth method. The concentration of ptyalin falls markedly about the sixtieth year of life. This reaction involves only the first step in the breakdown of starch to achroodextrin (amyloclastic action).

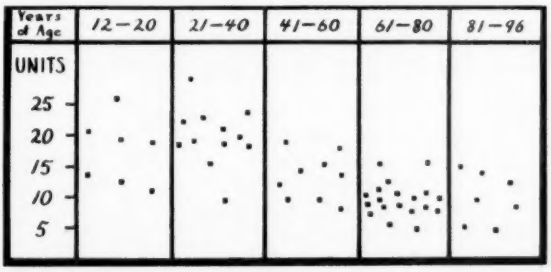

Chart 2.—Pancreatic amylase. This graph is rather similar to chart 1 *A*, except that the units are much less. It is obvious from the chart that the aged need suffer no embarrassment of carbohydrate digestion.

We determined the values for free and total acid as well as for pepsin in all cases. In about 35 per cent of the younger subjects and in about 65 per cent of the aged subjects there was no free acid in the "fasting" gastric contents. Occasionally we found a relatively high value for pepsin, but we could not find any correlation between the concentrations of acid and pepsin in "fasting" gastric juice. We found a steady drop in acidity with advancing age. Similar observations have been published by Bloomfield,[8] Sagal, Marks and Kantor [9] and others. Mullins and Flood [10] found a high correlation between acid and pepsin secretion in response to a test meal, though exceptions were not infrequent. In general, a high value for acid was likely to be accompanied by a high

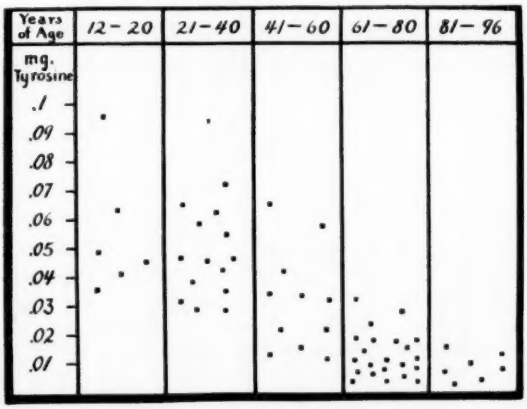

Chart 3.—Pepsin. The concentration falls sharply during the seventh decade of life and after that maintains a rather constant low value.

value for pepsin, and vice versa. According to our observations there was no evidence of such relations in "fasting" gastric juice.

The concentration of pepsin (chart 3) is low in old persons. In the younger group it shows great variability, but it has rather constant low values for old persons. Osterberg, Vanzant, Alvarez and Rivers [11]

8. Bloomfield, A. L.: The Mechanism of Decrease of Gastric Secretion with Advancing Years, Am. J. M. Sc. **190**:325, 1935.

9. Sagal, Z.; Marks, J. A., and Kantor, J. L.: The Clinical Significance of Gastric Acidity, Ann. Int. Med. **7**:76, 1933.

10. Mullins, C. R., and Flood, C. A.: A Study of Gastric Pepsin in Various Diseases, J. Clin. Investigation **14**:793, 1935.

11. Osterberg, A. E.; Vanzant, F. R.; Alvarez, W. C., and Rivers, A. B.: Studies of Pepsin in Human Gastric Juice, Am. J. Digest. Dis. & Nutrition **3**:35, 1936.

made analyses of gastric juice of 6,200 patients and our observations parallel theirs closely in that values for pepsin fluctuated widely in the cases of young persons. These authors found the secretion of pepsin to decrease with age much as does the secretion of acid.

The concentration of trypsin (chart 4) in our cases was similar to that of pepsin except that the values for the younger group did not show such extreme variations as in the case of pepsin and that a drop in the values after the fortieth year of life was observed.

Both proteolytic enzymes were present in the aged, in a concentration one fourth that in the control group. It is usually stated that the pancreas secretes when the gastric hydrochloric acid acts on the duodenal mucosa. We found no evidence of pancreatic hypofunction in cases of

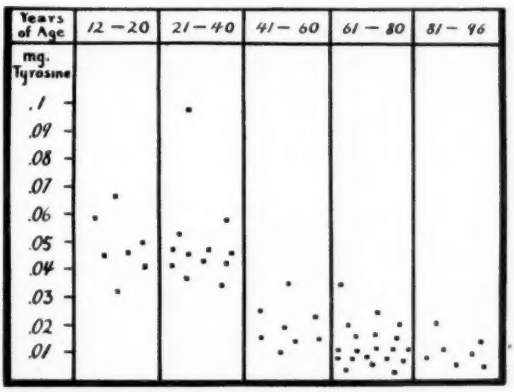

Chart 4.—Trypsin. The tryptic activity falls sharply after the fortieth year of life. The proteolytic powers of pancreatic juice bear no relation to gastric acidity.

achlorhydria or subacidity. This point may be illustrated by means of two typical protocols, one from the control and one from the old age group.

Relation of Gastric Acidity to Pancreatic Activity

	E. L., aged 42	N. S., aged 76
Free acid	0	0
Total acid	0	0
Pancreatic amylase	12 units	16 units
Pancreatic trypsin	0.034 mg.	0.006 mg.
Pancreatic lipase	3.35 cc.	2.42 cc.

In the first case the concentrations of the three enzymes were within normal limits; in the second case amylase and lipase showed normal values, trypsin being diminished but falling in line with our results for

old persons. McClure [12] stated that the normochylic reaction is characterized by an ample quantity of pancreatic juice of low enzyme concentration, whereas the achylic is characterized by a smaller quantity of juice of higher enzyme concentration. Calculating the average total quantity of trypsin, McClure concluded with regard to the digestive function that the secretion of duodenal juice both in the achylic and in the normochylic subject finally attains the same efficiency.

It should be emphasized that in our own series enzyme activity, determined on fasting persons, showed no correlation between gastric acidity and trypsin concentration. The main determinant of the activity of trypsin is apparently age. McClure's subjects were fed a bread meal to stimulate duodenal secretion, and the trypsin concentration was

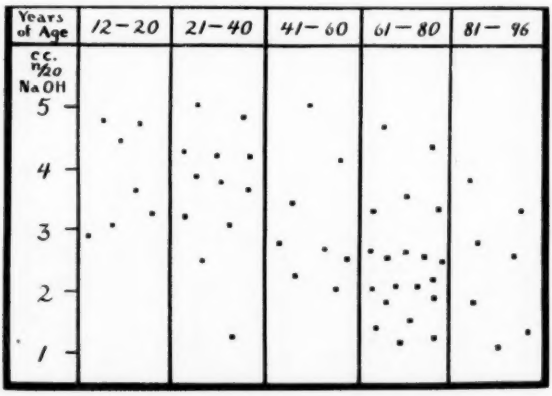

Chart 5.—Pancreatic lipase. The lipolytic activity of pancratic juice is variable and is dependent neither on gastric acidity nor on the age of the subject.

apparently conditioned by the gastric acidity. In view of our own findings in fasting subjects, his conclusions may be subject to some doubt. Furthermore, the values for trypsin obtained by us showed the maximum enzyme activity of each individual sample, since the analytic method employed avails itself of the optimum p_H for the reaction.

It is known that the concentration of lipase in pancreatic juice is subject to great variation. This also is in keeping with our results. We found that the activity of lipase (chart 5) is slightly diminished in the aged, but it is unlikely that the diminished activity interferes with the hydrolysis of fat in the food.

12. McClure, C. W.: Functional Activities of the Pancreas and Liver: A Study of Objective Methods for the Estimation of Function Levels in Health and Disease, New York, Medical Authors' Pub. Co., 1937.

The average values for all enzymes for our female subjects, both old and young, were slightly lower than those for males.

There is no literature concerning the activity of enzymes in old age. In spite of the low concentration of the proteolytic enzymes indicated by our results, nothing has been written about special difficulties of old persons in the digestion of proteins. The problem of mastication often necessitates the use of a soft diet which is relatively high in carbohydrate and low in proteins. It is known that institutions for the aged serve a diet high in carbohydrate and low in proteins. As we have noted, the digestion of carbohydrates is not markedly disturbed in old persons. It is likely that, even though the concentration of proteolytic enzymes is low, it is adequate to meet the requirements of the small protein intake. We are aware from clinical experience that there are old persons whose protein intake is fairly large and who have no difficulty in digestion. It is possible that the character of the food may be a factor in the secretory response.

It would be of interest to determine the secretory responses to various types of food and to various stimulants of gastric and pancreatic secretion, such as histamine, alcohol, olive oil and secretin. This we hope to report in the future.

The question might be raised whether our results are due to physiologic changes or to gastritis, which may accompany old age. None of the subjects had a history of gastritis or symptoms indicating clinical gastritis; we therefore regard them as normal old persons. It would be extremely interesting to correlate our results with gastroscopic observations. This we hope to do at a future date.

SUMMARY

1. The fasting concentrations of salivary ptyalin, of gastric pepsin and of pancreatic amylase, trypsin and lipase were determined in a group of 32 subjects between 12 and 60 years of age and in a group of 29 subjects between 60 and 96 years of age.

2. Old persons show a deficiency in the concentration of salivary amylase and slightly subnormal values in the concentration of pancreatic amylase.

3. Both proteolytic enzymes (pepsin and trypsin) are diminished in the aged and therefore cannot compensate for each other.

4. The concentration of lipase was found to be relatively unchanged in old age.

5. Subacidity and anacidity did not influence either the activity of the proteolytic enzymes or the secretory action of the pancreas.

6. These studies may be important in the dietary management of old persons.

CLINICAL STUDIES IN CIRCULATORY ADJUSTMENTS

VI. PHYSIOLOGIC RELATION BETWEEN POSTURE AND CARDIAC OUTPUT

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When man assumed an upright posture he added appreciably to the adaptive needs of his circulation. New vasomotor regulations became necessary to counteract the effects of gravity. Inadequacies of these regulatory processes, whether congenital or acquired, are of importance to the clinician, who is confronted not infrequently with patients presenting untoward symptoms after a change in posture. Although the effects of gravity are greater on the venous than on the arterial side, there are so many factors which compensate for this primary effect on the venous return that the net change in the circulation produced by change in position can best be studied in terms of cardiac output. The reports in the literature on the effect of change of posture on cardiac output are so conflicting that a corroborative study of this subject by the highly satisfactory Grollman method was undertaken.

From the Medical Service of Dr. I. W. Held and the Laboratory Department of the Beth Israel Hospital.

This study was made possible through the establishment of a fund for this purpose by Henry W. Dazian.

MATERIAL AND METHOD

In the present study (the sixth in a series "Clinical Studies in Circulatory Adjustments"[1]), cardiac output after alteration of posture was determined for 6 normal subjects, 5 hypertensive subjects, 3 patients with neurocirculatory asthenia, 5 patients with organic heart disease (chronic cardiac valvular disease and disease of the coronary arteries) and 4 patients with anemia.

A modification of the Grollman acetylene method was utilized according to the specifications published in another paper by one of us.[1e] The Grollman method is preferable to others in that it is the simplest and the least objectionable to the patient.

The normal subjects were interns and laboratory attendants; the patients were from the inpatient and outpatient departments of the hospital. The tests were performed at least six to eight hours after the subject had eaten a meal, and the determinations were made with the subject in four positions: (1) recumbent, (2) with feet elevated, (3) sitting and (4) standing. The subject was kept in the recumbent position for an hour to allow an approach to a basal state; tight clothes were loosened and shoes removed; a small pillow was used to add to the comfort of this position. At the end of the hour the pulse, blood pressure and oxygen consumption were determined, followed by determination of the value for arteriovenous oxygen difference. After fifteen minutes the acetylene rebreathing was repeated. The patient's lower extremities were then elevated by raising the lower third of the bed to an angle of 45 degrees with the body. This position was maintained for thirty minutes, after which time the determinations were made; the rebreathing was repeated in fifteen minutes. This check was carried out with the subject in each position. Subsequently the subject was allowed to sit in a comfortable chair with the back supported for one-half hour, when the determinations again were made. After this the standing position was assumed for a thirty minute period. Whenever possible the tests were performed with the subject in the four positions. In some instances, however, it was necessary to shorten the procedure, omitting the sitting posture, since it represents an intermediate stage between the recumbent and the upright position. The study of the 23 subjects included a total of seventy-eight positions.

SUMMARY OF FINDINGS

Analysis of the 6 normal subjects (see table) showed that change of position had practically no effect on blood pressure. With the subject standing there was a slight increase in pulse rate. The cardiac output remained practically unchanged with all positions, but the cardiac stroke was diminished when the subject stood or assumed the position of recumbency with the feet elevated.

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1. (*a*) Goldbloom, A. A.; Libin, I., and Roht, P. K.: Clinical Studies in Circulatory Adjustments: I. Clinical Evaluation of Studies of Circulating Blood Volume, Arch. Int. Med. **55**:484 (March) 1935. (*b*) Goldbloom, A. A., and Bauer, H. E.: Clinical Studies in Circulatory Adjustments: II. Venous Pressure; a Simple Bedside Method, Collect. Papers New York Homeop. M. Coll. **1**:45, 1935. (*c*) Goldbloom, A. A., and Roht, P. K.: Clinical Studies in Circulatory Adjustments: III. Clinical Evaluation of Cardiac Output Studies, Internat. Clin. **3**:206, 1936. (*d*) Rothschild, M. A., and Goldbloom, A. A.: Clinical Studies in Circulatory Adjustments: IV. Obliterating Pulmonary Arteritis with Secondary Pulmonary Changes and Right Ventricular Hypertrophy; Report of a Case with Autopsy, Arch. Int. Med. **61**:600 (April) 1938. (*e*) Goldbloom, A. A., and Lieberson, A.: Clinical Studies in Circulatory Adjustments: V. Clinical Evaluation of Cardiodynamic Studies, Am. J. M. Sc. **197**:182, 1939.

The patients with hypertension had a slightly increased pulse rate in the standing and sitting positions. There was no significant change in cardiac output with the various positions. The cardiac stroke was slightly increased with elevation of the feet but was essentially unchanged with all the other postures.

The group of patients with neurocirculatory asthenia had an increased pulse rate in the sitting and standing positions. Cardiac output and cardiac stroke, however, were not significantly altered.

The patients with organic heart disease showed a slight increase in cardiac output in the upright positions, especially in the sitting posture. These findings

Average Values for Various Groups

Condition	Number of Subjects	Body Surface, Square Meters	Blood Pressure	Pulse Rate	Oxygen Consumption, Cc./Min.	Arteriovenous Oxygen Difference, Cc./Liter	Cardiac Output, Liters/Min.	Cardiac Output per Beat, Cc.	Cardiac Index, Liters
Normal	6	1.75							
Recumbent	..	....	110/70	73	228	58	3.99	53	2.28
Feet elevated	..	....	118/80	80	236	63	3.81	46	2.18
Standing	..	....	116/80	84	260	65	3.98	47	2.27
Sitting	..	....	105/69	76	242	60	4.01	52	2.29
Hypertension (compensated)	5	1.71							
Recumbent	..	....	180/106	82	244	59	4.14	50	2.42
Feet elevated	..	....	176/109	82	265	61	4.35	52	2.54
Standing	..	....	170/105	86	264	63	4.19	48	2.45
Sitting	..	....	176/107	85	277	64	4.34	50	2.54
Neurocirculatory asthenia	3	1.67							
Recumbent	..	....	114/63	79	213	56	3.80	47	2.27
Feet elevated	..	....	109/63	80	224	58	3.86	47	2.31
Standing	..	....	102/65	92	241	61	3.92	42	2.34
Sitting	..	....	110/71	89	236	58	4.06	45	2.43
Cardiac disease	5	1.75							
Recumbent	..	....	159/90	83	237	62	3.82	46	2.18
Feet elevated	..	....	165/89	82	247	61	4.12	51	2.35
Standing	..	....	161/82	85	246	60	4.16	49	2.37
Sitting	..	....	160/86	88	268	58	4.66	53	2.66
Anemias	4	1.68							
Recumbent	..	....	118/78	74	224	62	3.64	51	2.23
Feet elevated	..	....	123/81	73	243	67	3.70	50	2.27
Standing	..	....	115/77	78	225	58	3.84	49	2.35
Sitting	..	....	110/65	88	220	53	4.15	47	2.54

are based on limited determinations for the upright and sitting positions because of the orthopnea of the patients. Care must be exercised, therefore, in interpreting the results.

Patients with various types of anemia also failed to show any significant change in the cardiac output on change of position.

GENERAL COMMENT

When one assumes the upright position, gravity exerts an effect on both the arterial and the venous tree, but especially on the latter, with its comparatively low head of pressure. As Hess [2] has pointed out, the

2. Hess, W. R.: Die Gesetze der Hydrostatik und Hydrodynamik, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 7, pp. 888-933.

circulation is established to the advantage of the lower half of the body. The effect on the circulation is not marked if the venous side can maintain the return blood flow to the heart. Definite quantities of blood stagnate, however, in the lower extremities, as Atzler and Herbst [3] showed in their plethysmographic studies and Parrisius [4] with the capillary microscope. There is, furthermore, a diminution of the circulating blood volume with the body in the upright position, according to Eppinger,[5] the blood stagnating in the blood depots of the hepatic-splanchnic region and the subpapillary cutaneous plexus.

The increased difficulty of venous return caused by reducing the diastolic filling of the heart would normally result in a lessened cardiac output, according to Starling's "law of the heart." There are, however, several important physiologic mechanisms which compensate in great part for this drop in stroke volume. Perhaps the most important of these is the carotid sinus apparatus, which suffers a diminution of tone when the stroke volume and blood pressure in the aorta fall. This produces reflexly an increase in pulse rate and a narrowing of the peripheral arterioles, with a resultant rise in diastolic pressure. It is likely that an insufficient blood supply to the vasomotor centers of the medulla acts in conjunction with the carotid sinus reflex to produce these effects. Less known reflexes from muscles, tendons, articular surfaces and walls of blood vessels in the lower extremities also may play a role. Thus, a change from a prone to an upright posture produces normally an average rise of 10 to 12 pulse beats and 8 to 10 mm. of diastolic pressure, with a very slight drop (0 to 4 mm.) in systolic blood pressure at the brachial artery (Ghrist [6]).

In general, these compensatory mechanisms suffice in the normal person to prevent distress. When gravitational shock does occur in man, some other disturbance of the circulatory mechanism is present (Macleod [7]). One encounters gravitational shock clinically in soldiers who have been standing rigidly at attention for too long a period, in vasolabile persons, in patients convalescing from severe illness and in

3. Atzler, E., and Herbst, R.: Die Schwankungen des Fussvolumens und deren Beeinflussung, Ztschr. f. d. ges. exper. Med. **38**:137, 1923.

4. Parrisius, W.: Der Blutstrom in den Hautkapillaren in verschiedenen Körperregionen bei wechselnder Körperlage, Deutsches Arch. f. klin. Med. **141**: 243, 1922.

5. Eppinger, H.: Zur Pathologie der Kreislaufcorrelationen, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1931, vol. 16, p. 2.

6. Ghrist, D. G.: Circulation and Postural Change: Adjustments in Health and Disease, California & West. Med. **39**:161, 1933.

7. Macleod, J. J. R.: Physiology in Modern Medicine, ed. 8, edited by P. Bard, St. Louis, C. V. Mosby Company, 1938.

normal persons after vigorous exercise (Mateeff and Petroff [8]). It is usually explained as due to lack of the normal pumping action of the muscles and to ischemia of the vasomotor center because of reduced stroke volume.

There is also a distinct clinical group of patients with "postural hypotension" who have syncopal attacks on alteration of position (Herz;[9] Münzer;[10] Martini and Pierach;[11] Bradbury and Eggleston [12]). They sustain a marked drop in blood pressure on assuming the upright position, but the pulse rate remains slow and unchanged. Similar effects on blood pressure and attacks of syncope are frequently seen in cases of Addison's disease, but in this condition the pulse is usually rapid.

The effects of postural change are more marked than normally in persons with varicose veins or with acrocyanosis. Wollheim [13] has described such persons as presenting marked stasis in the subpapillary plexus, with consequent diminution in the circulating blood volume when the body is in the upright position.

From these clinical observations it would appear that gravity has an effect on the circulation which in the main is compensated for in the average person. When one comes to the more scientific study of this subject, however, one encounters a confusing picture. Historically the problem of alteration in cardiac output due to change in position was first approached through roentgen studies of the cardiac silhouette. Moritz,[14] Dietlen [15] Vaquez,[16] Groedel [17] and others reported smaller

8. Mateeff, D., and Petroff, C.: Gravitationsshock beim Menschen nach Muskelarbeit, Ztschr. f. d. ges. exper. Med. **85**:115, 1932.

9. Herz, M.: Ueber Bradykardie, Hypotonie und hypotonische Bradykardie, Wien. klin. Wchnschr. **23**:768, 1910.

10. Münzer, E.: Zur Lehre von den vaskularen Hypotonien, Wien. klin. Wchnschr. **23**:1341, 1910.

11. Martini, P., and Pierach, A.: Die niedere Blutdruck und der Symptomenkomplex der Hypotonie, Klin. Wchnschr. **5**:1857, 1926.

12. Bradbury, S., and Eggleston, C.: Postural Hypotension, Am. Heart J. **1**:73, 1925.

13. Wollheim, E.: Die zirkulierende Blutmenge und ihre Bedeutung für Kompensation und Dekompensation des Kreislaufs, Ztschr. f. klin. Med. **116**: 269, 1931.

14. Moritz, F.: Methodisches und Technisches zur Orthodiagraphie, Deutsches Arch. f. klin. Med. **81**:1, 1904.

15. Dietlen, H.: Ueber die klinische Bedeutung der Veränderungen am Zirkulationsapparate insbesondere der wechselnden Herzgrösse bei verschiedener Körperstellung (Liegen und Stehen), Deutsches Arch. f. klin. Med. **97**:132, 1909.

16. Vaquez, H.: Diseases of the Heart, translated by G. F. Landlaw, Philadelphia, W. B. Saunders Company, 1924.

17. Groedel, F. M.: Welche Momente bedingt die verschiedene Grösse respektive Form des vertikalen und des horizontalen Herzorthodiagrammes? Ann. d. städt. allg. Krankenh. zu München **14**:328, 1910.

measures of the heart shadow in orthodiagrams made when their subjects were in an upright position. This suggested a diminished volume of the heart, but it was not until methods of determination of cardiac output were perfected that conclusive data could be obtained to prove this. Lindhard,[18] using the nitrous oxide method, reported diminution of the cardiac output with the subject in the upright position, but his findings are of questionable value, as his determinations for the various positions were made on different days. Collett and Liljestrand [19] stated that they have confirmed Lindhard's findings, but they offered only a single experiment. Henderson [20] also reported a marked diminution in cardiac output with the subject in the upright position, but he used the ethyl iodide method, the results of which are questionable.

With the development by Grollman [21] of the acetylene method, more accurate determination of the effect of posture on cardiac output became possible. Grollman, in an intensive study, failed to find any appreciable change, but Kylin,[22] reviewing Grollman's figures found that they establish, at least statistically, a diminution of 0.21 liters (5 per cent) with the subject in the erect position. Kylin's own series indicates a diminution of 0.46 liters (11 per cent) with the subject in the erect position. Kroetz [23] found that the cardiac output with the subject in the prone position (average 4.42 liters) is greater than with the subject in the sitting posture (average, 3.5 liters) and is smallest of all with the subject in the erect position. Bielschowsky [24] and Fisher [25] have confirmed these findings.

Grollman ascribed the contradictory findings to the subjects' superficial breathing in the recumbent position, which, he contended, results in a poor mixture of the gases, with consequent lower arteriovenous oxygen differences and higher values for cardiac output. Fisher's

18. Lindhard, J.: Effect of Posture on Output of Heart, Skandinav. Arch. f. Physiol. **30**:395, 1913.

19. Collett, M. E., and Liljestrand, G.: Variations in the Resting Minute Volume of the Heart, Skandinav. Arch. f. Physiol. **45**:17, 1924.

20. Henderson, Y.: Efficiency of the Heart and Its Measurement: Applications and Results on Man, Lancet **2**:1215 and 1317, 1925.

21. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

22. Kylin, G.: The Relation Between Heart Volume and Stroke Volume in Recumbent and Rest Positions, Skandinav. Arch. f. Physiol. (supp.) **69**:237, 1934.

23. Kroetz, C.: Messung des Kreislaufminutenvolumens mit Acetylen als Fremgas, Klin. Wchnschr. **9**:966, 1930.

24. Bielschowsky, P.: Ueber den Einfluss des Lagewechsels insbesondere der Beinhochagerung auf das Minutenvolumen des Herzens bei gesunden und kranken Menschen, Klin. Wchnschr. **11**:1252, 1932.

25. Fisher, I. L.: Das Schlag- und Minutenvolumen des menschlichen Herzens bei verschiedenen Körperstellungen, Arbeitsphysiol. **6**:111, 1932.

results are questioned because of the variation in his values for oxygen utilization by the same patient in the same position on various days. Schellong,[26] like Grollman, has been unable to find significant changes in cardiac output and has ascribed the diminution found by other workers to changes due to the long period of standing required by the methods used. He found that the cardiac output drops on quiet standing, largely because of a drop in the rate of oxygen consumption.

Bock,[27] using a tilting table to eliminate the effect of muscular activity, obtained a 24 per cent diminution of cardiac output with the subject in the upright position. This was more marked in patients convalescing from various diseases (30 per cent) and still more noticeable in a group of vasolabile patients (34.6 per cent). Determinations on 3 trained patients revealed less diminution in cardiac output (i. e., from 3 per cent to 10 per cent), whereas in 1 subject, an athlete, there was actually an increase from 7.9 to 16.2 per cent. These findings are important in that they call attention to two significant factors in adaptation of the circulation to a change in position. These are muscular activity and the condition of the patient as influenced favorably by training or adversely by disease. Diverse results in the literature may conceivably be due to varying degrees of muscular activity and differing states of physical fitness in "healthy" subjects or of inaccuracies introduced by the stringent requirements of the experimental procedure, which interfere with the free play of the patient's compensatory mechanisms.

CONCLUSION

It has been our purpose in this study to determine whether alteration of posture produces a definite change in cardiac output. A number of authors have reported a marked effect on cardiac output due to change in position; others have reported little effect. Using the Grollman acetylene method with 23 subjects (normal persons, hypertensive persons, patients with cardiac disease and patients with various anemias and blood dyscrasias), we found little, if any, change in the cardiac output on change of position. Our results are in close agreement with those obtained by Grollman.

The conclusion is reached that the practically unaltered cardiac output demonstrated by the subjects studied in four different postures is indicative of the ability of the human organism under natural circumstances to compensate for the changes induced by the force of gravity.

26. Schellong, F.: Klinische Untersuchungen über Kreislaufregulation in aufrechter Körperstellung, Verhandl d. deutsch. Gesellsch. f. Kreislaufforsch., 1933, p. 176. Schellong, F., and Heinemeier, M.: Ueber die Kreislaufregulation in aufrechter Körperstellung und ihre Störungen, Ztschr. f. d. ges. exper. Med. **89**:49 and 61, 1933.

27. Bock, H. E.: Das Minutenvolumen des Herzens im Liegen und Stehen, Ztschr. f. d. ges. exper. Med. **92**:782, 1934.

Progress in Internal Medicine

ALLERGY

A REVIEW OF THE LITERATURE OF 1939

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Last year I [1] wrote: "Each year the papers written on allergy cover a wider territory." Now the situation is becoming even more complicated because it appears that certain symptoms, like asthma, may come from causes which are not allergy at all, though the clinical pictures seem to be quite the same as in the typical cases of allergy. "All is not allergy that wheezes," and, by the same token, sneezes and itches of various kinds which seem like allergy may not be due to allergy in the ordinary clinical sense. In a recent discussion of the relation between anaphylaxis and allergy, Dragstedt [2] points out that whereas histamine, heparin and possibly other agents are liberated easily from sensitive cells as a result of the specific antigen-antibody reaction, the same substances may be released from normal cells which have been acted on by nonantigenic material. Evidently it is possible to tie the various parts of the picture together.

The incidence of allergy is always impressive, and one wonders whether the present high figures represent a fundamental change in the reaction of the population to modern life or whether they depend simply on the fact that physicians and laymen are becoming "allergy conscious." Service [3] finds that major allergic diseases can be found in 20 per cent of the general population and that 16 per cent have more than one allergic symptom. Norgaard [4] writes that in Denmark about 200,000 patients with bronchial asthma are invalided each year, in a country which has a population of only 3,500,000. In other words,

1. Rackemann, F. M.: Allergy: Review of Literature of 1938, Arch. Int. Med. **63**:173 (Jan.) 1939.

2. Dragstedt, C. A.: Anaphylaxis and Allergy, Ann. Int. Med. **13**:248, 1939.

3. Service, W. C.: The Incidence of Major Allergic Diseases in Colorado Springs, J. A. M. A. **112**:2034 (May 20) 1939.

4. Norgaard, A.: Die soziale Bedeutung von Asthma bronchiale und eine Untersuchung des Nutzens bei einer Veränderung von Erwerb und Wohnort, Acta med. Scandinav., 1938, supp. 89, p. 113.

something over 5 per cent of the population suffers from asthma alone, and nothing is said about hay fever, eczema or urticaria. Less alarming, however, are the low figures of Stoesser and Shaperman.[5] In a total of 2,771 new admissions to the clinic in Minneapolis in a period of two years, there were only 141 cases of allergy, or 5 per cent. All of these figures are interesting, but they and others like them vary widely according to many circumstances hard to control, and the plain fact is that allergic diseases are very common and so are worthy of careful consideration.

ANAPHYLAXIS

As I have emphasized in previous reviews, the difference between the guinea pig and the rat is striking. The former is easy to sensitize; the latter is hard to sensitize. In the meantime, the Kopeloffs[6] produced anaphylaxis in the monkey easily, first with horse serum and then with egg white. Precipitins, the Arthus phenomenon and typical Dale-Schultz reaction were all described in the treated monkeys. The "alarm reaction," so disconcerting to the demonstration of anaphylactic shock in the guinea pig, is described by Karady and his associates.[7] When the sensitized pigs were treated with formaldehyde, or were cooled to a temperature of 1 C. for five hours or were made to walk in revolving cages, they became resistant to the subsequent shock. They survived the reinjection which killed all of the controls. Evidently, the preceding treatment had served to increase the resistance, obviously in some nonspecific manner, and the observation can be correlated no doubt with the important clinical experience that rough treatment of various kinds, notably fever and surgical operation, as well as full etherization, has a markedly beneficial, though temporary, effect on the course of human asthma. The recognition of the "alarm reaction" is timely. Another animal experiment is that of Molomut,[8] who found that removal of the hypophysis from a rat can be accomplished with reasonable ease and renders the animal so treated subject to fatal anaphylactic shock without causing any change in the production of circulating antibodies.

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5. Stoesser, A. V., and Shaperman, E.: The Care of the Allergic Child, Minnesota Med. **18**:292, 1935.

6. Kopeloff, L. M., and Kopeloff, N.: Anaphylaxis in the Rhesus Monkey: I. Horse Serum as an Antigen, J. Immunol. **36**:83, 1939; II. Egg White as an Antigen, ibid. **36**:101, 1939.

7. Karady, I.; Selye, H., and Browne, J. S. L.: The Influence of the Alarm Reaction on the Development of Anaphylactic Shock, Orvosi hetil. **82**:681, 1938; abstracted, J. Immunol. **35**:335, 1938.

8. Molomut, N.: The Effect of Hypophysectomy on Immunity and Hypersensitivity in Rats with a Brief Description of the Operative Technic, J. Immunol. **37**:113, 1939.

CHEMISTRY OF ALLERGY

A number of new reports show that the skin can be sensitized to a great variety of substances which are nonprotein and have relatively simple chemical structures. These will be discussed later in the section on diseases of the skin. Here, however, must be mentioned one or two interesting papers. Newell and his associates [9] report a study of the protein in the Prausnitz-Küstner antibody. The Tiselius apparatus consists of a U tube that contains the solution to be tested, and through it is passed an electric current. The different protein constituents move through the tube at different rates of speed until eventually they become separated. This separation is shown by changes in concentration which produce deflection in a beam of light and so make it possible to observe different bands or shadows in the light between the protein fractions. With this method, Newell found that the Prausnitz-Küstner antibody is all in that globulin fraction which was designated as gamma by Tiselius. This gamma globulin is an important constituent of the pseudoglobulin of serum, for other experiments have shown that most other antibodies, like precipitins and agglutinins, are contained in it. The point is that the Prausnitz-Küstner antibody is chemically analogous to other antibodies, for example, the antibody in antipneumococcus serum.

The chemistry of allergens is always important. Studies on ragweed will be described later under the subject of hay fever. In a comprehensive article, Weiss [10] has indicated the close relationship between biologic action and chemical structure. In 1937, Nitti and his co-workers,[11] in Paris, pointed to the importance of the precise chemical structure of allergens, saying that guinea pigs could be sensitized regularly by paraphenylenediamine but not by the ortho or meta isomers. Furthermore, when the amino group was replaced by an acetyl or a hydroxyl group the sensitizing power was lost. Spies, Bernton and Stevens [12] have studied the chemistry of the cottonseed embryo. An extract in distilled water was boiled and the coagulant removed and discarded. The filtrate was centrifuged, and to it alcohol was added to a final concentration of 75 per cent. The sticky, dark-colored precipitate was then dissolved in distilled water and was found to give a good cutaneous

9. Newell, J. M.; Sterling, A.; Oxman, M. F.; Burden, S. S., and Krejci, L. E.: Electrophoretic Separation of the Antibody from Human Allergic Serum, J. Allergy **10**:513, 1939.

10. Weiss, S.: Chemical Structure: Biological Action; Therapeutic Effect, New England J. Med. **220**:906, 1939.

11. Nitti, F.; Bovet, D., and Depierre, F.: Les phénomènes allergiques provoques par certaines amines aromatiques, Rev. d'immunol. **3**:376, 1937.

12. Spies, J. R.; Bernton, H. S., and Stevens, H.: The Chemistry of Allergens: Isolation of Active Fraction from Cottonseed, J. Allergy **10**:113, 1939.

reaction. Later, however, it was purified further by treatment with basic lead acetate and alcohol, which resulted in another precipitate. From this second filtrate the lead salts were removed by hydrogen sulfide, and the final material was precipitated by another treatment with 75 per cent alcohol. This second alcohol precipitate was dried and later taken up in water to make the solution several times as active as the original alcohol precipitate. It gave a Molisch reaction to carbohydrate and on hydrolysis a positive reaction with Benedict's solution. Treatment with trinitrophenol caused a heavy precipitate which gave negative reactions for carbohydrate. Solutions of this precipitate, however, produced cutaneous reactions which were quite as large as those with the original purified material. The authors attribute the allergenic properties to the protein rather than to the carbohydrate components.

Meantime, Abramson, Sookne and Moyer [13] present a complicated study of electrical properties of ragweed, the results of which indicate that the "skin-reactive" constituent is protein-like in nature and that its isoelectric point lies between p_H 3.9 and p_H 4.3. An important contribution to the chemistry of allergy is the observation of Winkenwerder, Buell and Howard [14] that patients with skin sensitivity to ragweed also give positive cutaneous reactions to the nucleic acids and their derivatives, including the crystalline nucleotides adenine, guanine and cytosine, and to simple purine salts like adenine sulfate, xanthine nitrate and sodium urate. Severe constitutional reactions were produced in 2 patients with doses as small as 0.02 mg. of adenine nucleotide. The fact that only an occasional reaction to these substances was observed in a group of 40 normal persons leads to the interesting query: Does ragweed contain nucleic acid, and if so are the cutaneous reactions to ragweed dependent on the nucleic acid component?

IMMUNOLOGY

The mechanism of the so-called desensitization treatment of hay fever has been studied further. It will be recalled that in 1935 Cooke, Barnard, Hebald and Stull [15] injected mixtures of ragweed and ragweed-sensitive serum into the skin of normal persons. When the serum was obtained before treatment, the antibody in this A serum was neutralized by the ragweed. The mixture produced a one hour reaction, but it

13. Abramson, H. A.; Sookne, A. M., and Moyer, L. S.: Electrokinetic Phenomena: The Inactivation of Ragweed Pollen Extracts by Adsorption and the Electric Charge of the Resultant Surface, J. Allergy **10**:317, 1939.

14. Winkenwerder, W. L.; Buell, M. V., and Howard, J. E.: Preliminary Studies on the Sensitizing Properties of the Nucleic Acids and Their Derivatives, Science **90**:356, 1939.

15. Cooke, R. A.; Barnard, J. H.; Hebald, S., and Stull, A.: Serological Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy (Hay Fever), J. Exper. Med. **62**:733, 1935.

failed to transfer the ragweed sensitiveness to the skin of a normal recipient. With the P serum obtained after treatment, on the other hand, there was no immediate reaction and yet passive transfer was successful. The authors concluded that in the second case there had developed a new mechanism by which the reaction between the allergen ragweed and the passive transfer antibody, the "reagin," had been inhibited. A new inhibiting antibody was described. This work has been confirmed by Harley,[16] in England, and more recently by Langner and Kern.[17] Incidentally, Harley found that if after a few days the sites in the recipient's skin were tested with ragweed again, the reaction then became positive, thus showing that the attachment of the reaction-inhibiting substance to the antibody was not stable. In a later paper, Cooke, Loveless and Stull [18] found that volunteers who had been treated repeatedly with mixtures of ragweed extract and ragweed-sensitive serum failed to show any serologic changes. In another group, however, larger amounts of ragweed without sensitive serum were given, and in this group serologic changes did occur and were found to be similar to those observed in the ragweed-sensitive patients after successful treatment; that is, there were inhibition of the immediate reaction and successful passive transfer. The combination of the sensitive serum and the ragweed was inhibited, and by a factor which was later found to occur in the pseudoglobulin, no doubt the gamma globulin fraction of the serum already discussed. Langner and Kern [17] repeated the experiment with precisely the same technic and obtained precisely the same results. In addition, these authors describe a new form of treatment. They obtained serum from patients with hay fever who had been treated successfully by the ordinary method and dried it by the so-called lyophile process—a rapid freezing and dehydration *in vacuo* at low pressure. This dried serum was then taken up in half the original quantity of water and was injected intramuscularly into patients with active symptoms. Moderate malaise often resulted, but the relief from hay fever was complete in 9 of 11 patients. However, in 3 patients the relief did not continue for longer than a week. To control their experiments, the authors injected normal serum treated in the same manner but obtained no results. More recently, Sherman and Stull [19] studied the serum

16. Harley, D.: Hay Fever: Effect of Pollen Therapy on Skin Reactions; Reaction-Inhibiting Substance in Serum of Treated Patients, J. Path. & Bact. **44**:589, 1937.

17. Langner, P. H., and Kern, R. A.: Studies on the Immunology of Hay Fever, J. Allergy **10**:1, 1938.

18. Cooke, R. A.; Loveless, M., and Stull, A.: Studies on Immunity in Type of Human Allergy (Hay Fever): Serologic Response of Nonsensitive Individuals to Pollen Injections, J. Exper. Med. **66**:689, 1937.

19. Sherman, W. B., and Stull, A.: Serological Changes Resulting from the Treatment of Hay Fever Over a Period of Years, J. Allergy **10**:465, 1939.

of 55 patients at the end of their treatment. Passive transfer failed entirely in 9 of them, and the response was weak in 30 others. Of the 29 untreated patients, however, 22 showed good transfers. Furthermore, it was found that with successive years of treatment there was a qualitative change in the character of the antibody. The ability to transfer sensitiveness diminished, while the ability to neutralize the ragweed increased. Schmidt and Lippard [20] also studied the effect of pollen treatment on the concentration of the passive transfer antibody. Constant amounts of serum were incubated with different amounts of antigen, and the mixtures were used to sensitize the recipients' skin. The more antigen that was required to neutralize the antibody and so to prevent the passive transfer reaction, the stronger was the serum. They found that the titer increased after treatment, but with no particular relation to the amount of treatment, that is, to the largest dose tolerated. In many cases, the titer rose to more than tenfold its pretreatment level. In another paper, Lippard and Schmidt [21] studied the changes in antibody (reagin) titer which occurred in children sensitive to a food after the ingestion of that food. They found that there was an increase but that it varied in amount. This increase seemed to indicate that the rising titer of antibody was a protective mechanism, and it was in accord with the observation that after the first feeding the children could take the same food with less clinical difficulty.

Several papers concern the transfer of anaphylactic sensitiveness from animals to the human skin. First, Eagle, Arbesman and Winkenwerder [22] have reviewed the literature and reopened the question of the antigenicity of ragweed in animals. Using four types of extract of short ragweed pollen without preliminary alum precipitation and without the use of adjuvant antigens, they found that fatal anaphylaxis could be produced regularly in guinea pigs by both active and passive sensitization and that precipitating and complement-fixing antibodies could be produced in high titer in rabbits. (In their extracts, the total nitrogen varied between 0.60 and 1.05 mg. per cubic centimeter.) In the following paper [23] they showed that some of the rabbit antiserums

20. Schmidt, W. M., and Lippard, V. W.: Human Passive Transfer Antibody: III. Serial Titrations on Treated and Untreated Patients with Hay Fever, Am. J. Dis. Child. **56**:550 (Sept.) 1938.

21. Lippard, V. W., and Schmidt, W. M.: Human Passive Transfer Antibody: IV. Studies on Children Hypersensitive to Foods, Am. J. Dis. Child. **56**: 797 (Oct.) 1938.

22. Eagle, H.; Arbesman, C. E., and Winkenwerder, W. L.: The Production in Experimental Animals of Antibodies to Short-Ragweed Pollen (Precipitation, Complement-Fixation, and Anaphylaxis), J. Immunol. **36**:425, 1939.

23. Winkenwerder, W. L.; Eagle, H., and Arbesman, C. E.: On the Presence in Rabbit Antisera vs. Ragweed Pollen of Skin-Sensitizing Antibodies Passively Transferable to Man, J. Immunol. **36**:435, 1939.

were capable of transferring the sensitiveness to the human skin. However, the transfer ability was not parallel with the precipitin content. Sherman, Stull and Hampton [24] made a similar experiment on guinea pigs and found that the serum from half their animals could sensitize human skin without difficulty, but that the intensity of the subsequent test reaction was not as great as that produced by the serums of acutely sensitive human beings.

SERUM DISEASE

This year there are a number of reports which call attention to the involvement of the nervous system in serum disease. Neuritis is not an uncommon sequel. It develops apparently from compression of the nerves by the perineural edema. Bennett [25] has made a careful study of the literature and adds 5 cases. Hoagland [26] and Meszaros [27] each observed a case. Iritis is reported by Theodore and Lewson.[28] Finally, cerebral manifestations, including loss of consciousness, aphasia and partial paralysis, are described in papers by Lemierre [29] and by Kennedy and his associates.[30]

Abdominal symptoms may complicate serum sickness. Clog [31] reports a case in which surgical intervention revealed swelling of the mesenteric glands and marked hyperemia of the peritoneum.

Various treatments for serum disease have been advised. Voss and Hundt [32] used convalescent serum from patients recently recovered from serum disease, and in so doing made an interesting observation.

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24. Sherman, W. B.; Stull, A., and Hampton, S. F.: Passive Sensitization of Human Skin by Serum of Experimentally Sensitized Animals, J. Immunol. **36**: 447, 1939.

25. Bennett, A. E.: Horse Serum Neuritis, with Report of Five Cases, J. A. M. A. **112**:590 (Feb. 18) 1939.

26. Hoagland, R. J.: Neuritis Following Serum Administration, Mil. Surgeon **82**:134, 1938.

27. Meszaros, K.: Durch Tetanusschutzimpfung verursachte Neuritis, Deutsche Ztschr. f. d. ges. gerichtl. Med. **30**:45, 1938.

28. Theodore, F. H., and Lewson, A. C.: Bilateral Iritis Complicating Serum Sickness, Arch. Ophth. **21**:828 (May) 1939.

29. Lemierre, A.: Un cas de manifestations cérébrales de la maladie sérique, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:827, 1938.

30. Kennedy, F.; Wortis, S. B., and Wortis, H.: Clinical Evidence for Cerebral Vasomotor Changes, New York State J. Med. **38**:1441, 1938.

31. Clog, M. L.: Syndromes douloureux abdominaux au cours de la maladie sérique, Bull. Soc. pédiat. de Paris **36**:354, 1938.

32. Voss, E. A., and Hundt, O.: Das Prinzip der inversen Anaphylaxie als Methode des Antikörpernachweises beim Menschen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **94**:281, 1938. Voss, E. A.: Inverse Anaphylaxie beim Menschen zugleich ein Beitrag zur Problematik der Ueberempfindlichkeitserscheinungen beim Menschen, Ztschr. f. Kinderh. **59**:612, 1938.

When this serum, full of antibodies for horse serum, is injected into a child several days after a dose of horse serum, interesting reactions occur which the authors describe as "inverse" anaphylaxis and which increase in severity as the time of treatment after the original dose of horse serum becomes longer. If the convalescent human serum is given within the first three days, a small wheal and erythema appear at the site of injection of the horse serum, but if given after the fourth day, the local wheal spreads to a general rash. If the convalescent serum is delayed until the eighth or ninth day, a general shocklike reaction may result. However, when these reactions have subsided, the serum disease improves. One should note, however, that the course of serum disease is usually short anyway.

Histaminase will be discussed later. Meantime, Foshay and Hagebusch [33] have used it in treatment of serum disease and have found it helpful. Eight patients were given the tablets by mouth and 6 were relieved in from seven to thirty-six hours. Twelve patients were treated with intramuscular doses of histaminase and 11 were relieved. For prophylaxis, the authors recommend that 4 or 5 tablets containing 5 units each be given three times a day, beginning at the time of injection of the prophylactic serum.

An interesting observation is that of Fleisher and Jones,[34] who found that the addition of sodium hydroxide to serum, followed by warming to 55 C. and subsequent neutralization, prevented the development of serum disease in rabbits. Unfortunately, the preparations were toxic for many animals, and so the method can hardly be applied to the prevention or treatment of serum disease in man.

HAY FEVER

New pollen surveys are reported by Deamer and his associates [35] for the country north of San Francisco, by Cole [36] for Ames, Iowa, and by Metzger [37] for the west coast of Florida. There is little ragweed in Florida.

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33. Foshay, L., and Hagebusch, O. E.: Histaminase in the Treatment of Serum Sickness, J. A. M. A. **112**:2398 (June 10) 1939.

34. Fleisher, M. S., and Jones, L. R.: Serum Sickness in Rabbits: VII. A Method for Removing or Destroying the Factor Causing Serum Sickness, J. Immunol. **36**:511, 1939.

35. Deamer, W. C.; Jenkins, H. L., and Lazarus, D. S.: Pollen Survey: Report on Arcata District, Humboldt County, California, California & West. Med. **49**:450, 1938.

36. Cole, J.: A Pollen Survey in Ames, Iowa, in 1938, J. Iowa M. Soc. **29**: 198, 1939.

37. Metzger, F. C.: The Climatic Treatment of Hay Fever and Asthma, with Special Reference to Florida, J. A. M. A. **112**:29 (Jan. 7) 1939.

The antigenic relationships of different pollens have been studied further. Hampton, Stull and Cooke [38] tested the uterus of guinea pigs sensitized to alum-precipitated ragweed for reactions to other pollens at the same time. Uterine strips which reacted to the specific pollen with a large contraction reacted to the related pollen in 17 of 38 tests. In other words, the experiment indicated an antigenic relationship, but not identity, of the pollens used. The authors worked not only with the low and giant ragweeds but with the three common grasses timothy, orchard grass and June grass as well. With a different technic, Prince and Secrest [39] studied the relations between ragweed and marsh elder. Using the serum of patients sensitive to both weeds, they passively sensitized sites on the skin of normal recipients and then desensitized these sites by treatment, first with ragweed and then with marsh elder pollen. When the sites were exhausted with ragweed, they still responded to marsh elder, but when exhausted with marsh elder they were exhausted for ragweed at the same time. Here again was a close, though not absolute, relationship.

Another sort of investigation concerns the standardization of pollen extracts—the determination of their potency. Arbesman and Eagle [40] point out that each of the present methods for the assay of extracts is open to criticism and that true values must wait for an adequate chemical identification of the active principle. They describe the variables concerned in the experiments of passive transfer, which are many and difficult to control.

Stull and Sherman [41] present further evidence to support Cooke's finding that the allergenic strength of pollen extracts depends primarily on the content of protein nitrogen.

The treatment of hay fever has been discussed this year chiefly in relation to oral therapy. Zeller [42] reviews the history: In 1922 Touart treated 6 patients with good results, and in the same year Solomon had similar experiences. In 1927 Black showed that ragweed antigen could

38. Hampton, S. F.; Stull, A., and Cooke, R. A.: Antigenic Studies by the Dale Test: I. The Antigenic Relationship of Certain Pollens, J. Allergy **10:** 417, 1939.

39. Prince, H. E., and Secrest, P. G., Jr.: Immunological Relationship of Giant, Western, Common Ragweed and Marsh Elder (Iva Ciliata), J. Allergy **10:**537, 1939.

40. Arbesman, C. E., and Eagle, H.: The Assay of Ragweed Pollen Extracts, J. Allergy **10:**521, 1939.

41. Stull, A., and Sherman, W. B.: Further Studies on the Allergenic Activity of Protein and Nonprotein Nitrogen Fractions of Ragweed Pollen Extract, J. Allergy **10:**130, 1939.

42. Zeller, M.: Oral Ragweed Pollen Therapy, J. Allergy **10:**579, 1939.

be demonstrated in the blood stream and urine after the taking of pollen by mouth, and in 1928 his report on the oral treatment of 71 patients was enthusiastic. In 1929 he was less enthusiastic. Now, in 1939, Black [43] has treated 40 patients, who were sensitive to ragweed and who applied for treatment during the week before the onset of the hay fever season, with doses of the dried pollen by mouth. Good results, however, were obtained in only 12 patients, or 40 per cent—a low figure. It is interesting that as soon as the oral treatment was started, Black noted that the hypodermic doses could be increased without causing the large local reactions observed before the oral doses had been given. Other reports on oral treatment are conflicting. Rockwell [44] treated 182 patients, with good results in 63 per cent. Bernstein and Feinberg,[45] however, treated 20 patients coseasonally, with good results in only 2. The discussion of Zeller's paper, which was read before the Association for the Study of Allergy in May 1939, was particularly interesting, for it concerned chiefly the question of absorption of the ingested pollen. The chief evidence for absorption is the immediate reaction which occurs in the skin of ragweed-sensitive patients when the serum drawn from a patient soon after the taking of pollen by mouth is injected into it. As Feinberg said, human serum of many types causes immediate reactions which are hard to interpret, but at least they are nonspecific. However, as Black said in his discussion: "It seems inconsistent to say that the antigen is not absorbed and then to say that the patient developed asthma and hay fever as the result of the absorption." Whereas the whole subject is controversial, the evidence so far indicates that oral therapy is not beneficial, and so the Chicago Society of Allergy has urged that the commercial promotion of oral pollen therapy should be deferred in the interest of the public and the general practitioner until further experimentation now in progress has been reported.

Meantime, the constitutional reactions which constitute a great danger in pollen therapy have been studied by Greene,[46] who has reviewed the literature and analyzed the cases in the series which he and I have studied.

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43. Black, J. H.: The Oral Administration of Ragweed Pollen, J. Allergy **10**:156, 1939.

44. Rockwell, G. E.: Clinical Results in the Prevention and Treatment of Hay Fever by Oral Administration of Pollens of the Grass and Ragweed Types, Ohio State M. J. **34**:784, 1938.

45. Bernstein, T. B., and Feinberg, S. M.: Oral Ragweed Pollen Therapy: Clinical Results of Experiments on Gastro-Intestinal Absorption, Arch. Int. Med. **62**:297 (Aug.) 1938.

46. Greene, J. E.: Constitutional Reactions in Hay Fever Therapy, M. Clin. North America **23**:1255, 1939.

FUNGOUS SPORES

Durham [47] presents further information on the high incidence of airborne fungous spores in this country. Pratt [48] has made a careful study of the mold spores in the air of Boston. He exposed Petri dishes out of doors for a half-hour each day for a year and found that Alternaria, Hormodendrum and non-spore-bearing molds increase in summer while Aspergillus and Penicillium have no seasonal incidence. In his experience, these molds are of considerable practical importance, for 25 per cent of 177 children with seasonal asthma and hay fever reacted to Alternaria in cutaneous and passive transfer tests, and when they were treated with this mold, with and sometimes even without pollen treatment at the same time, the results were good.

Grain smuts and rusts are emphasized by Wittich,[49] who found them to be the principal cause of trouble in 8 cases. Harris [50] reported 13 cases of the same sort. The patients gave a history of hay fever or asthma in the presence of the grain smuts. Furthermore, Harris was able to reproduce the symptoms by instilling the grain dust or the smuts into the patient's nostril. In another paper, Harris [51] reported that whereas the common molds, like Alternaria, bore no antigenic relationship to extracts of wheat or oat, nevertheless wheat smuts could be neutralized by wheat dust and vice versa, the technic being that of the ordinary desensitization of passively sensitized skin sites. Meantime, Henrici [52] found that Aspergillus fumigatus contains an endotoxin poisonous for guinea pigs. When an extract from the finely ground mycelium mass was injected subcutaneously, there developed massive edema with necrosis and ulceration, and when it was given intravenously, it caused fatty changes in the liver and necrosis of the kidney tubules as well as hemolysis. This study was made on guinea pigs, but it goes to show that not all of the mold extracts can be used with impunity.

VASOMOTOR RHINITIS

Chronic vasomotor rhinitis, with the pale, boggy swelling of the nasal mucous membrane and symptoms which are very troublesome

47. Durham, O. C.: Incidence of Air-Borne Fungus Spores: II. Hormodendrum, Alternaria and Rust Spores, J. Allergy **10**:40, 1938; An Unusual Shower of Fungus Spores, J. A. M. A. **111**:24 (July 2) 1938.

48. Pratt, H. N.: Mold Spore Content of the Air in Boston, with Reference to Atopic Sensitivity, J. Pediat. **14**:234, 1939.

49. Wittich, F. W.: Further Observations on Allergy to Smuts, Journal-Lancet **59**:382, 1939.

50. Harris, L. H.: Allergy to Grain Dusts and Smuts, J. Allergy **10**:327, 1939.

51. Harris, L. H.: The Nature of the Grain Dust Antigen: Crossed Reactions to Grain Dusts and Smuts, J. Allergy **10**:433, 1939.

52. Henrici, A. T.: An Endotoxin from Aspergillus Fumigatus, J. Immunol. **36**:319, 1939.

because of their persistence, needs much further study. Winkenwerder and Gay [53] have analyzed 198 cases and found that house dust, feathers and orris powder were responsible in 95 per cent, with infections of the sinuses important in only 22 cases (11 per cent). In a rather stormy article, Piness and Miller [54] object to the indiscriminate removal of tonsils from those children who suffer from repeated colds and bronchitis and who have allergy as the essential cause of their trouble. A million and a half tonsillectomies are performed in the United States each year, and the operation seems to have little effect on the subsequent development of hay fever or asthma, for the figures for the development of allergy are the same for the group with tonsillectomy as for the group with the tonsils still in place.

Meantime, Hoseason,[55] in England, has an interesting observation on vasomotor rhinorrhea with asthma, saying that nasal congestion is one of the specific cutaneous responses to the estrogens which circulate during estrus. The rhinorrhea is apt to be worse immediately before menstruation, and asthma may supervene at that time. Treatment, however, is not discussed except to say that zinc ionization is the simplest and most effective method. Another English report is that of Wilson-Pepper and Royle,[56] who found that one injection of progesterone, the corpus luteum hormone, controlled the symptoms in a woman who suffered from menorrhagia and marked spasmodic rhinorrhea.

ASTHMA

Asthma is usually due to allergy. In most cases, a careful history will reveal the nature of the causative factor. In diagnosis, cutaneous tests are important, and several papers appear on them. It always seems curious to me that whereas many men test their patients with hundreds of substances, including many foods, reports on the results of tests with foods are unusual and deal chiefly with the more common articles—eggs, wheat, milk and fish. Dusts, on the other hand, are of great practical importance as a cause of asthma in adults (much greater than foods), and so one finds references to a wide range of pollens, to the animal danders, to a variety of occupational dusts and to a number of

53. Winkenwerder, W. L., and Gay, L. N.: Perennial Allergic Rhinitis: An Analysis of One Hundred and Ninety-Eight Cases, Bull. Johns Hopkins Hosp. **61**:90, 1937.

54. Piness, G., and Miller, H.: Allergy of the Upper Respiratory Tract in Infancy and Childhood, J. A. M. A. **113**:734 (Aug. 19) 1939.

55. Hoseason, A. S.: Vasomotor Rhinorrhea, with Asthma, Associated with Menstruation, Brit. M. J. **2**:703, 1938.

56. Wilson-Pepper, J. K., and Royle, H.: Progesterone and the Nasal Mucosa, Brit. M. J. **1**:974, 1939.

materials in household furniture. Withers'[57] paper is therefore of interest. He studied 20 patients clinically sensitive to one or more foods, including, besides the cereals, the bean and tomato families. He found 91 patients with positive clinical sensitiveness, and yet only half of these had accompanying positive cutaneous reactions. On the other hand, of 65 patients with negative clinical reactions, 31 had positive cutaneous reactions—again nearly half. His evidence makes it clear that clinical observations are much more satisfactory than are the direct or the indirect method of testing.

Cow's milk is one of the important items. Although his latest paper is not yet published, Hill's[58] studies on milk are significant. When a normal infant first drinks cow's milk, precipitins develop in the blood in ten days, and also there is a positive reaction to the intracutaneous test for milk, though never to the scratch test. After two to three weeks, however, the cutaneous reaction fades, while the circulating antibodies, precipitins and complement-fixing bodies continue for many months and then slowly disappear. Allergy to milk shows itself in reactions of three kinds. The first and most common is eczema, with its typical distribution on the face, neck and cubital and popliteal spaces. It is properly called "atopic eczema." Sixty per cent of babies with eczema give positive responses to lactalbumin, while only 17 per cent react to casein at the same time. The last observation explains the fact that the substitution of goat's milk is not always followed by clearing of the eczema, for goat casein is the same as cow casein. Milk is really two foods instead of one, and the fact is not ordinarily recognized. The second type of reaction to milk consists of gastrointestinal symptoms, with or without asthma at the same time. Colic and pylorospasm are said to be due to milk in rare cases. The third type of reaction is also rare and consists of an anaphylactic-like shock which occurs when the breast-fed baby is given his first feeding of cow's milk. The time interval is probably a deciding factor in the character of the reaction. The baby with eczema has, on the chances, taken a quart (about 950 cc.) of milk every day, whereas the baby who reacts with shock had trouble on the first feeding of milk. From Scandinavia comes a similar series of observations by von Sydow.[59] He recognized a group of infants who reacted to milk with eczema and asthma and were not amenable to desensitization and another group with gastrointestinal symptoms who subsequently did acquire tolerance to milk.

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57. Withers, O. R.: Food Allergens: II. Atopic Reagins and the Botanical Classification of Foods, J. Allergy **10**:105, 1939.

58. Hill, L. W.: Milk as an Allergen, personal communication to the author.

59. von Sydow, G.: Some Cases of "Cow's Milk Idiosyncrasy." Acta pædiat. **23**:383, 1939.

The old question of the difference between raw food and cooked food in the production of symptoms, and also as the source of cutaneous test material, has been aired. On the one hand, Ratner and Gruehl [60] found that guinea pigs given injections of raw cereal products show a high sensitivity, whereas heating destroys the sensitizing power. On the other hand, Malkin and Markow,[61] in their clinic, made cutaneous tests with raw and with cooked foods side by side and found that in 92 per cent of their cases the reactions were the same. It is tempting to doubt whether any of their reactions were of clinical significance.

Tobacco presents an interesting problem, with various authors holding different points of view. It is interesting that Peshkin and Landay [62] have found that the cutaneous reaction to tobacco occurs more commonly in patients who are sensitive to pollen, either of grass or of ragweed. Harkavy [63] reviews the recent literature.

INTRINSIC ASTHMA

Last spring, at the meeting of the Association for the Study of Allergy in St. Louis, I [64] pointed out that "all is not allergy that wheezes," and on the same program was a paper by Alexander,[65] entitled "Allergic Syndromes in the Absence of Allergens." If all the cases of asthma are studied together, it appears that in about 25 per cent of them a careful history will not reveal a possible relation to diet or environment. In the relatively clean environment of the hospital, even in an oxygen tent, the asthma continues. Furthermore, the deaths from asthma which I have observed have occurred only in this group with intrinsic asthma. Of 283 patients, 20 have died of asthma—a proportion of 8.2 per cent. In this group with intrinsic asthma the cause of trouble is much in doubt. Clinical experience suggests that the symptoms be designated as part of an "asthma syndrome" rather than as mere "asthma," for with the asthma in these cases go several rather characteristic features. Diseases of the paranasal sinuses occur in at least three fourths of the cases, in most of which operations on sinuses have already been done, without

60. Ratner, B., and Gruehl, H. L.: Anaphylactogenic Properties of Certain Cereal Foods and Breadstuffs, Allergenic Denaturation by Heat, Am. J. Dis. Child. **57**:739 (April) 1939.

61. Malkin, J. I., and Markow, H.: An Analysis of the Comparative Results of Skin Testing with Cooked and Uncooked Foods: Preliminary Report, J. Allergy **10**:337, 1939.

62. Peshkin, M. M., and Landay, L. H.: Cutaneous Reactions to Tobacco Antigen in Allergic and in Non-Allergic Children, with Direct and Indirect (Local Passive Transfer) Methods of Testing, Am. J. Dis. Child. **57**:1288 (June) 1939.

63. Harkavy, J.: Tobacco Skin Reactions and Their Clinical Significance, J. Invest. Dermat. **2**:257, 1939.

64. Rackemann, F. M.: Intrinsic Asthma, J. Allergy, to be published.

65. Alexander, H. L.: Allergic Syndromes in the Absence of Allergens, read before the Society for the Study of Allergy, St. Louis, May 16, 1939.

benefit to the asthma. Eosinophilia is characteristic. Malaise is prominent (Vaughan has called it "allergic toxemia"). Finally, Greene and I [66] have reported on an interesting subgroup of patients with asthma who were found to suffer also from periarteritis nodosa. It becomes important, therefore, to study the physiology of asthma and to learn about other conditions which are accompanied by the symptom of wheezing. In the fatal cases in our series, autopsy showed two types of lesion. In 18 instances the bronchi were filled with tough, sticky plugs, sufficient to cause death by suffocation. In the other 2 cases, however, plugs were not observed, and the lungs were not so distended; the cause of death was evidently concerned with a physiologic or functional spasm of the muscles in the smaller bronchi rather than with obvious mechanical plugging of their lumen.

Prickman and Moersch [67] have had wide experience with bronchoscopy in treatment of asthma. Of 83 consecutive asthmatic patients, they found stenosis of one or more of the bronchi in 40 per cent. Balyeat and Seyler [68] say that in severe asthma there are two factors, one being sensitization, the other a chemical factor, and that the symptoms depend on local edema of the mucosa of the bronchial tubes, which in turn depends on a chronic infection. The trouble with the infectious theory is that, in my cases at least, absence of any pathologic evidence of infection was one of the striking features.

Friedman and Molony [69] comment on the role of allergy in atelectasis and describe 6 cases in which plugs producing bronchial occlusion could be removed through the bronchoscope, with great benefit. They found that the occlusions were due to allergy. On the other hand, Schneider [70] describes a case of a 9 month old child who had occlusion of a bronchus from pressure of tuberculous lymph nodes and whose condition had been diagnosed erroneously as bronchial asthma. In many of our patients who died of intrinsic asthma local areas of collapse were observed at autopsy, and it is surprising that the complication does not occur, or at least is not recognized, more often. If masses of sticky mucus can plug the bronchi partially by a ball valve mechanism to produce emphysema, it is easy to believe that they can also plug them completely

66. Rackemann, F. M., and Greene, J. C.: Periarteritis Nodosa and Asthma, Tr. A. Am. Physicians **54**:112, 1939.

67. Prickman, L. E., and Moersch, H. J.: Asthma and Its Association with Bronchostenosis, M. Clin. North America **23**:961, 1939.

68. Balyeat, R. M., and Seyler, L. E.: Dual Etiology of Intractable Asthma, J. Oklahoma M. A. **32**:49, 1939.

69. Friedman, T. B., and Molony, C. J.: Role of Allergy in Atelectasis in Children, Am. J. Dis. Child. **58**:237 (Aug.) 1939.

70. Schneider, L. V.: Bronchial Occlusion Due to Tuberculous Lymphadenitis, Am. Rev. Tuberc. **38**:320, 1938.

to produce atelectasis; if the argument is carried a bit further, one can understand how the atelectasis may lead to bronchiectasis.

Watson and Kibler [71] studied 46 cases of bronchiectasis and found sinusitis in 67 per cent and asthma in 32 per cent. Their statement that "the common association of sinusitis and bronchitis can be explained on the basis of allergy" is interesting and is comparable with the earlier suggestion of Kern and Schenck [72] that nasal polyps were of allergic origin. In both instances I agree with the premises, but I should like to substitute the term "asthma syndrome" for that of "allergy."

In 1932, Loeffler [73] described local infiltrations, *Frühinfiltrate,* which were found by roentgen examination in patients, usually children, suffering from mild respiratory symptoms. The patients were not sick, and the lesions were found to clear usually within a few weeks. The eosinophils in the blood were increased, often to 10 per cent, but the author said nothing of asthma. Tuberculosis, tumor and abscess could each be excluded in the differential diagnosis. This year there are four reports [74] on "Loeffler's syndrome" (by Breton, Cohen, Soederling and Weber, respectively), and each of them suggests that the cause is allergy. These reports fit well the conception of local atelectasis due to bronchial occlusion as a transient process, dense enough to cast a shadow in the roentgenogram, and evidently much more common than has been appreciated. Evidently, too, the process can occur even in cases of relatively mild asthma, for the reports available do not emphasize the life and death struggle which I have seen in the hospital.

According to Cole and Cole,[75] silicosis is accompanied by dyspnea, often simulating asthma. Here, however, the symptoms depend on capillary occlusion which involves large localized areas of the lung, accompanied by compensatory capillary dilatation in other regions.

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71. Watson, S. H., and Kibler, C. S.: The Role of Allergy in Bronchiectasis, J. Allergy **10**:364, 1939.

72. Kern, R. A., and Schenck, H. P.: Importance of Allergy in Etiology and Treatment of Nasal Mucous Polyps, J. A. M. A. **103**:1293 (Oct. 2) 1934.

73. Loeffler, W.: Zur Differential-Diagnose der Lungeninfiltrierungen: I. Frühinfiltrate unter besonderer Berücksichtigung der Ruckbildungzeiten, Beitr. z. Klin. d. Tuberk. **79**:338, 1932; II. Ueber flüchtige Succedan-Infiltrate (mit Eosinophilie), ibid. **79**:368, 1932.

74. Breton, A.: A propos de la radiologie de l'asthme. Le syndrome de Löffler, Paris méd. **1**:538, 1938. Cohen, R.: Le syndrome de Loeffler (Infiltrations pulmonaires fugaces avec éosinophilie), Presse méd. **46**:797, 1938. Soederling, B.: Transient Lung Consolidations in Asthmatic Children with Reference to Eosinophilia, Arch. Dis. Childhood **14**:22, 1939. Weber, F. P.: Transient Pulmonary Infiltration with Blood Eosinophilia (Loeffler's Syndrome), Brit. J. Child. Dis. **36**:15, 1939.

75. Cole, L. G., and Cole, W. G.: Dyspnea of Silicosis, J. A. M. A. **113**: 1216 (Sept. 23) 1939.

Bilharzial asthma is another interesting disease which fits in with the conception that "all is not allergy that wheezes," the term "allergy" being used in the sense of hypersensitiveness to dusts or foods. Four cases have been presented by Mainzer.[76] The disease is a schistosomiasis of the lungs. The spleen is large. There is fever, and the eosinophil count may be as high as 60 or 70 per cent, with high white cell counts. Roentgenograms show striations throughout the pulmonary fields. The treatment is easy, for when antimony is given the asthma clears and the eosinophils decrease. The author believes that the asthma is an allergic reaction to the products of the worms or their eggs and is not due to anatomic changes in the lung. These lesions persist long after the asthma has gone, and, furthermore, they are common whereas asthma is a rare complication of the disease.

Every one interested in asthma and in all questions pertaining to the pulmonary circulation should examine carefully the fascinating study of the pulmonary circulation by Robb and Steinberg.[77] Diodrast is a chemical which contains approximately 50 per cent of iodine and which, being water soluble, has been used for intravenous pyelography. The authors have demonstrated that if roentgenograms of the chest are taken within a few seconds after the intraveous injection of diodrast, shadows of the various chambers of the heart and large blood vessels can be obtained. The reproductions of roentgenograms in their article are good enough to convey an excellent idea of the anatomy of these large vessels and something of their pathology.

Further information on the state of pulmonary circulation can be obtained by finding the circulation time. The method and the results are explained by Plotz,[78] who used the taste produced by intravenous injection of ether to measure the arm to lung time and the flush produced by intravenous administration of sodium cyanide to measure the arm to carotid time. The difference is the "left heart" time.

Cardiac asthma and the diseases of the pulmonary system of arteries, such as Ayerza's disease, which are often difficult to diagnose during life, should not be neglected in the list of conditions which can give rise to the symptom asthma. So also should be included emphysema. There is evidence not only that emphysema is a secondary development, resulting from chronic pulmonary disease, including asthma, but that "primary

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76. Mainzer, F.: Bilharzial Asthma: A New Type of Allergic Bronchial Asthma, J. Allergy **10**:349, 1939.

77. Robb, G. P., and Steinberg, I.: Visualization of the Heart and the Thoracic Blood Vessels in Pulmonary Heart Disease: A Case Study, Ann. Int. Med. **13**:12, 1939.

78. Plotz, M.: Asthmatoid Heart Failure: A Form of Left Ventricular Failure and Its Differentiation from Bronchial Asthma by Circulation Time and Other Criteria, Ann. Int. Med. **13**:151, 1939.

idiopathic emphysema" is a disease entity of considerable practical and theoretic importance. It is entirely proper to maintain that "all is not allergy that wheezes."

NOSE AND THROAT

Lesions of the nose and throat are common in asthma, as already stated. The recent literature has been well reviewed by Hansel,[79] but two papers deserve special attention. Francis and Stuart-Harris[80] infected ferrets with epidemic virus intranasally and then followed the progress of the disease by pathologic sections of the nasal mucous membrane of animals killed at various intervals. Their article is full of excellent pictures which show the development of the exudate, with sloughing of the whole surface on the second day and beginning of repair on the fourth day, and the changes in the character of the epithelium, culminating in the reestablishment of cilia on the tenth day. In a subsequent paper, they show that the epithelium in the process of repair and regeneration is unusually resistant to reinfection and physicochemical changes. Reinoculation with the virus produced only a structureless exudate, and ionization performed on the eighth day after infection caused little damage. Later, however, on the twenty-eighth day, ionization produced the usual severe reaction. The article is an excellent exposition of the manner in which the nasal mucosa behaves after injury. The second paper is one by Semenov[81] on the surgical pathology of nasal disease. This paper, too, has many excellent photographs of pathologic specimens which demonstrate the various changes that lead to thickening of the membrane, formation of cysts, inclusion of small foci of infection and formation of polyps—a timely study.

Meantime, and somewhat against my theory that nasal lesions are a part of the picture and not a cause of it, are the 2 cases cited by Bourne[82] in which injuries to the nasal septum were the precipitating factor in the production of asthma in predisposed persons. In both patients the asthma completely disappeared in one year and in two months, respectively, after submucous resection had been performed.

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79. Hansel, F. K.: Allergy as Related to Otolaryngology and Ophthalmology: Literature for 1938, J. Allergy **10**:187, 1939.

80. Francis, T., Jr., and Stuart-Harris, C. H.: Studies on the Nasal Histology of Epidemic Influenza Virus Infection in the Ferret: I. The Development and Repair of the Nasal Lesion, J. Exper. Med. **68**:789, 1938; II. The Resistance of Regenerating Respiratory Epithelium to Reinfection and to Physiochemical Injury, ibid. **68**:803, 1938.

81. Semenov, H.: The Surgical Pathology of Nasal Sinusitis, J. A. M. A. **111**:2189 (Dec. 10) 1938.

82. Bourne, W. A.: Asthma as a Sequel of Nasal Injury, Brit. M. J. **1**:870, 1939.

HISTAMINE

Interest continues in the theory that histamine may be the common denominator through which a variety of exciting causes can produce asthma. In his Bancroft Memorial Lecture, Kellaway,[83] of Australia, reviews the work on histamine as the effector set free by cellular injury. Recent titles under histamine in the *Quarterly Cumulative Index Medicus* indicate the many agents which can cause liberation of histamine: trypsin, curare, irritating vapors, fish poison, snake venom, anaphylactic shock and the Shwartzman reaction. Clinical studies on histamine are going on at the present time in at least five laboratories in this country. Unfortunately, the reports have not all appeared. The work is immensely difficult, chiefly because the amount of histamine present in the blood of patients with asthma is so small that it can be detected only by biologic methods, which are cumbersome and difficult. Abramson and Ochs [84] suggest that a modification of the ordinary cutaneous test to which histamine reacts promptly might give useful information. By using an electric current, they have been able to force histamine through the skin of man and animals and have found that by the method histamine can be detected in a concentration of less than 1 : 1,000,000. The article includes a number of interesting experiments in which a known quantity of histamine was added to the blood of rabbits and guinea pigs and could later be "recovered" with considerable accuracy. Evidently the method is sound as it is also simple. Farmer [85] has been able to treat guinea pigs with histamine in such a way that the uterine strip is insensitive to the amount of antigen (horse serum) that causes a good contraction in untreated controls. Furthermore, the histamine treatment renders the strip less sensitive to histamine itself, and so in another paper [86] he calls the effect desensitization. He observed it also when the guinea pigs were given doses of histamine by mouth. Perla [87] found that the injection of sterile solution of sodium chloride intraperitoneally into rats a few hours before an intraperitoneal dose of histamine enabled the animals to tolerate twice the normal lethal amounts.

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83. Kellaway, C. H.: Bancroft Memorial Lecture: Cellular Response to Injury, M. J. Australia **2**:447, 1938.

84. Abramson, H. A., and Ochs, I.: Skin Reactions: VI. A Simple Micromethod for the Assay of Histamine in Mammalian Blood, J. Lab. & Clin. Med. **24**:398, 1939.

85. Farmer, L.: Nonspecific "Desensitization" Through Histamine, J. Immunol. **36**:37, 1939.

86. Farmer, L.: Experiments on Histamine-Refractoriness: II. Nonspecific "Desensitization" Through Oral Application of Histamine, J. Immunol. **37**:321, 1939.

87. Perla, D.: Effect of an Excess of Salt on Resistance to Histamine in Rats, Proc. Soc. Exper. Biol. & Med. **41**:234, 1939.

As mentioned in the section on "Serum Disease," histaminase was found by Foshay and Hagebusch [33] to be useful in treatment of this condition. In 1930, Best and McHenry [88] showed that simple saline extracts of various animal organs when used fresh and untreated had the property of destroying the histamine in a solution to which they were added. Thus, an extract of 20 mg. of moist kidney could destroy 40 mg. of histamine in seventy-two hours. They found that almost every tissue contains an enzyme called histaminase. This year, Rose and Browne [89] have studied the question of what happens to histamine when it is injected intravenously. In rats, they injected histamine intravenously in amounts equivalent to 0.16 mg. per gram of body weight, and then killed the animals at intervals and studied their tissues. In other experiments they had shown that the organs were not capable of destroying histamine, but now they find that the content falls off sharply within thirty to sixty minutes after the injection. This is true of all the organs, with one important exception. The kidney takes up histamine much faster than other organs, the content in fifteen minutes being 480 micrograms, as compared with 79 micrograms for the liver and 64 micrograms for the lung. The authors believe that the increased amount of histamine in the blood represents merely the transport of all the histamine to the kidney, from which it can later be redistributed or disposed of. The point is that histaminase does not represent the only method by which histamine is eliminated. One wonders whether Perla's findings just mentioned may not depend on increased circulation following the injection of solution of sodium chloride; in the same sentence one can point to the good effect of the intravenous use of a solution of sodium chloride on asthma as possibly having a similar basis. There is much to be learned about histamine and so-called histaminase.

TREATMENT OF ASTHMA

The treatment of asthma in the ordinary case is to be conducted on a purely allergic basis, and it is not surprising to have Curschmann,[90] in Germany, and Salen, Hulting and Nordenfors,[91] in Sweden, report excellent results from the use of an allergen-free environment. Unfor-

88. Best, C. H., and McHenry, E. A.: The Inactivation of Histamine, J. Physiol. **70**:349, 1930.

89. Rose, B., and Browne, J. S. L.: The Distribution and Rate of Disappearance of Intravenously Injected Histamine in the Rat, Am. J. Physiol. **124**: 412, 1938.

90. Curschmann, H.: Aussichten der Asthmabehandlung im "allergenfreien Milieu," Fortschr. d. Therap. **14**:561, 1938.

91. Salen, E. B.; Hulting, C., and Nordenfors, B.: Bericht über die Tätigkeit am Heim für asthmakranke Schulkinder in Stockholm, Acta med. Scandinav., 1935, supp. 89, p. 85.

tunately, however, in the group of cases of intrinsic asthma management is not so easy. Last year, Keeney [92] published a preliminary report on the use of epinephrine base in oil—"slow epinephrine" as he called it. Now comes the complete report in a paper by Keeney, Pierce and Gay.[93] Many patients have been relieved for periods up to sixteen hours by the injection of 0.5 to 1.5 cc. In the symptomatic treatment of hay fever, Keeney [94] finds epinephrine in oil effective. Murphy and Jones [95] have also used the preparation, which they say is "of value." Spain, Strauss and Fuchs [96] have suggested another method by which the absorption of epinephrine can be delayed. They recommend that epinephrine be mixed with a 1 : 500 dilution of gelatin, which, being a nontoxic, nonantigenic substance, is harmless to the patient and, like peanut oil, is absorbed slowly. Brown [97] has a paper on theophylline with ethylene diamine, a drug which I agree is useful in treatment of patients with severe asthma who have become refractory to epinephrine. Magnesium sulfate is suggested by Haury,[98] who through experiments on isolated lungs of guinea pigs found that the drug produces bronchodilatation of from 20 to 45 per cent. Farmer [99] suggests ethyl carbamate, which he has given by mouth to 30 patients with asthma, in doses of 2 to 4 Gm. per day. The attacks were alleviated in 14 of 30 cases. Balyeat [100] does well to warn against the use of morphine in treatment of asthma, which I also find in most cases to do more harm than good. Not only does morphine abolish the cough reflex and depress the respiratory center, as Balyeat claims, but patients may be actually sensitive to morphine, as I have found in several cases.

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92. Keeney, E. L.: A Slowly Absorbed Epinephrine Preparation, Bull. Johns Hopkins Hosp. **62**:227, 1938.

93. Keeney, E. L.; Pierce, J. A., and Gay, L. N.: Epinephrine in Oil: A New, Slowly Absorbed Epinephrine Preparation, Arch. Int. Med. **63**:119 (Jan.) 1939.

94. Keeney, E. L.: Epinephrine in Oil: Its Effect in the Symptomatic Treatment of Hay Fever, J. Allergy **10**:590, 1939.

95. Murphy, J. A., and Jones, C. A.: Slow Epinephrine in the Treatment of Chronic Asthma, J. Allergy **10**:215, 1939.

96. Spain, W. C.; Strauss, B. A., and Fuchs, A. M.: A Slowly Absorbed Gelatin-Epinephrine Mixture, J. Allergy **10**:209, 1939.

97. Brown, G. T.: Aminophyllin in Asthma, J. Allergy **10**:64, 1938.

98. Haury, V. G.: The Broncho-Dilator Action of Magnesium and Its Antagonistic Action (Dilator-Action) Against Pilocarpine, Histamine and Barium Chloride, J. Pharmacol. & Exper. Therap. **65**:58, 1938.

99. Farmer, L.: The Use of Urethane in Symptomatic Treatment of Bronchial Asthma, J. Lab. & Clin. Med. **24**:453, 1939.

100. Balyeat, R. M.: Morphine: Dangerous Drug in Chronic Asthma, New Orleans M. & S. J. **91**:556, 1939.

Helium is still used. Barach [101] has treated a large series of patients, with good results. Now, Maytum [102] and Metz, Wearner and Evans [103] agree that inhalations of mixtures of helium and oxygen are useful in cases of status asthmaticus chiefly to restore the effectiveness of epinephrine. More recently, however, Barach [104] has written about oxygen, claiming that the inhalation of pure, 100 per cent oxygen for short periods has been of great benefit to certain patients with chronic emphysema. The same subject is discussed by Boothby, Mayo and Lovelace,[105] who emphasize the virtues of oxygen in treatment of asthma and other conditions.

Epinephrine is always of great practical value. However, it is well to note that there are reports of 2 cases in which serious trouble followed its use. Keeney [106] has described a man of 33, sensitive to ragweed, who had mild asthma in late August and was treated with a 1 : 100 dilution of epinephrine hydrochloride as a spray. Later, however, he was given a dose of epinephrine hydrochloride (0.5 cc. of the 1 : 1,000 solution) subcutaneously and immediately headache and coma developed, which were later found to be due to a large lesion in the left hemisphere involving the visual pathways and causing complete right hemiplegia. Gormsen,[107] in Sweden, described the case of a man of 42 with severe asthma who also was treated with the epinephrine spray. Inadvertently, he filled his hypodermic syringe not with the 1 : 1,000 but with the 1 : 100 solution of epinephrine, and in a few minutes after the injection he died. Acute epinephrine intoxication has been described before, and Gormsen found 28 cases in the literature. The minimum lethal dose for subcutaneous injection seems to be about 10 mg. of epinephrine. Meantime, Galgiani, Proescher, Dock and Tainter [108] found that when the membranes of rabbits and cats were sprayed with epinephrine each

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101. Barach, A. L.: The Use of Helium in the Treatment of Asthma and Obstructive Lesions in Larynx and Trachea, Ann. Int. Med. **9**:739, 1935.

102. Maytum, C. K.: Helium-Oxygen Mixtures in Status Asthmaticus, J. Allergy **10**:264, 1939.

103. Metz, C. W.; Wearner, A. A., and Evans, A. E.: Therapeutic Use of Helium, South. M. J. **32**:34, 1939.

104. Barach, A. L.: Physiological Methods in the Diagnosis and Treatment of Asthma and Emphysema, Ann. Int. Med. **12**:454, 1938.

105. Boothby, W. M.; Mayo, C. W., and Lovelace, W. R.: One Hundred Per Cent Oxygen, J. A. M. A. **113**:477 (Aug. 5) 1939.

106. Keeney, E. L.: Hemiplegia Following Injection of Epinephrine Hydrochloride, J. A. M. A. **112**:2131 (May 27) 1939.

107. Gormsen, H.: A Case of Fatal Epinephrine Intoxication, Ugesk. f. læger **101**:242, 1939.

108. Galgiani, J. V.; Proescher, F.; Dock, W., and Tainter, M. L.: Local and Systemic Effects from Inhalation of Strong Solutions of Epinephrine, J. A. M. A. **112**:1929 (May 13) 1939.

day for three months, the trachea showed loss of cilia and desquamation of the epithelium.

A year ago potassium chloride was suggested by Rusk and Kenamore [109] as a drug useful in treatment of urticaria. Since then, Rusk, Weichselbaum and Somogyi [110] have studied the concentration of potassium in the blood serum in various allergic states and have found it high. Whereas the average normal content is 19.5 mg. per hundred cubic centimeters, in urticaria it is 23.4 mg. and in asthma 23.6 mg., and during acute asthma it is 24.4 mg. The blood is merely the medium of transport. The authors' theory is that in allergy the potassium moves from the cells to the blood and that the good effects of insulin and of dextrose in cases of urticaria and of asthma depend on driving potassium back into the cells. By providing an excess of potassium in the diet, the cells can regain their normal potassium content. Meantime, Bloom [111] claims to have produced striking improvement in 29 patients with hay fever by giving them 25 grains (less than 2 Gm.) of potassium chloride per day by mouth. On the other hand, Cohen [112] treated 8 patients with chronic urticaria with the diet and the doses of potassium chloride recommended by Rusk and Kenamore, but in no case was improvement shown.

Cyclopropane anesthesia has been used in cases of severe intractable asthma by Meyer and Schotz,[113] who claim dramatic results in 1 case and describe two advantages: first, that the drug works rapidly, and, second, that the anesthetic mixture contains a high concentration of oxygen.

Roentgen treatment has been revived by Maytum and Leddy,[114] who have applied it to 161 patients. Marked relief was obtained in only 24 per cent of the patients treated with roentgen rays alone. Others did well, but they had other treatment at the same time.

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109. Rusk, H. A., and Kenamore, B. D.: Urticaria: A New Therapeutic Approach, Ann. Int. Med. **11**:1838, 1938.

110. Rusk, H. A.; Weichselbaum, T. E., and Somogyi, M.: Changes in Serum Potassium in Certain Allergic States, J. A. M. A. **112**:2395 (June 10) 1939.

111. Bloom, B.: The Use of Potassium Salts in Hay Fever: Preliminary Report, J. A. M. A. **111**:2281 (Dec. 17) 1938.

112. Cohen, A. E.: The Treatment of Chronic Urticaria with a High Protein, Low Sodium, Acid-Ash Diet, with Added Potassium Chloride; Case Reports, J. Allergy **10**:61, 1938.

113. Meyer, N. E., and Schotz, S.: The Relief of Severe Intractable Bronchial Asthma with Cyclopropane Anesthesia: Report of Case, J. Allergy **10**:239, 1939.

114. Maytum, C. K., and Leddy, E. T.: Roentgen Treatment of Asthma, J. Allergy **10**:135, 1939.

Operations on the sympathetic nerves have been described in previous reviews, and now it is interesting to have Leriche and Fontaine [115] report on the late results of stellectomy. They have followed 14 patients, all of them for at least two years and many for a much longer time, and have found that unilateral stellectomy performed on 7 patients resulted in virtual cures in 2 cases, 1 of the patients having been well for thirteen years. Bilateral stellectomy was performed on 7 patients, and 4 of them appear to be "cured."

DRUG ALLERGY

Drug allergy deserves increasing attention chiefly because of the advances in chemistry which have resulted in the exposure of an ever increasing number of persons to an ever larger number of new chemical substances, some of which are found in the large chemical industries while others appear in paints and varnishes, in cleaning fluids and solvents, in fuels, in solutions for photography, in cosmetics and, most important of course, in the host of new drugs or isomers of old drugs which have been recommended as improved remedies for all manner of human ills. Osborne and Jordon [116] say that almost any chemical will produce sensitization, and it therefore becomes important to do everything possible to prevent its development—for example, by the control of industrial dusts and by the better selection of persons to work in contact with them, through exclusion of those with allergic tendencies. Downing [117] has reviewed 2,000 cases of cutaneous eruptions occurring among industrial workers during the past six years. Schwartz [118] states that 1 per cent of the industrial workers in this country are affected each year, persons with oily skins being the most liable. The causative factors are widely distributed but are most important in the metal industry, with domestic and food industries following, in that order. The list of substances to which sensitiveness has been observed is remarkable, as may be seen in the presentation of Rostenberg and Sulzberger,[119] whose list of substances used in patch

115. Leriche, R., and Fontaine, R.: Les résultats éloignés au traitement chirurgical de l'asthme bronchique par la stellectomie, Strasbourg méd. **98**:475, 1938.

116. Osborne, E. D., and Jordon, J. W.: The Practical Aspect of the Prevention of Industrial Dermatoses, J. A. M. A. **111**:1533 (Oct. 22) 1938.

117. Downing, J. G.: Cutaneous Eruptions Among Industrial Workers: Review of Two Thousand Claims for Compensation, Arch. Dermat. & Syph. **39**:12 (Jan.) 1939.

118. Schwartz, L.: The Incidence of Occupational Dermatoses and Their Causes in the Basic Industries, J. A. M. A. **111**:1523 (Oct. 22) 1938.

119. Rostenberg, A., Jr., and Sulzberger, M. B.: A List of Substances for Patch-Testing, and the Concentrations to Be Employed, J. Invest. Dermat. **2**:93, 1939.

tests covers twenty pages of small type. The recent literature contains additional references to a variety of industrial substances which have been responsible for the dermatitis observed in a number of cases. Any list of these would be out of date by the time it is printed, and so will not be given here. However, several references are interesting. Burckhardt [120] describes bricklayers' dermatitis in 80 patients who reacted to patch tests and were sensitive to the calcium hydroxide in the lime. Others reacted to the tricalcium aluminate in the cement. Bakers' dermatitis has been studied by Zündel and Jentsch,[121] who found reactions to various persulfates, spice oils and turpentine among the 450 patients studied. It is curious that wheat sensitiveness was not mentioned.

Sulfanilamide has resulted in allergic manifestations, as expected. Tedder [122] reports three types of toxic manifestations, one of which depends on true sensitivity to the drug. Hallam [123] reports the case of a young man who had taken small doses of sulfapyridine for the treatment of urethritis and then was exposed to an ultraviolet lamp. The photosensitivity resulted in severe inflammation of the skin with edema and vesicles. Gallagher [124] presents the interesting case of a youth of 18 who was treated with sulfanilamide for a sore throat. Two years later, at the age of 20, he acquired acute urethritis and was again given sulfanilamide, in a new dose of 20 grains (1.3 Gm.). That afternoon, he had malaise, headache and fever, and on the third day was covered with a diffuse rash. His white cell count fell from 17,000 to 9,000. Another interesting case is reported by Rogers.[125] A woman, known to have skin sensitivity to various local anesthetics, was treated with sulfanilamide, whereon each and every site in which local anesthetics had been administered previously flared up with a bright erythematous reaction. Rogers points out that aminobenzene is the base common to sulfanilamide and to many local anesthetics.

Karaya gum is of particular importance because it is found so often not only in cosmetics but in domestic and kitchen materials. Bowen [126] adds 5 cases of sensitiveness to this substance.

120. Burckhardt, W.: Das Maurerekzem (Eine experimentelle und klinische Studie zur Ekzemfrage), Arch. f. Dermat. u. Syph. **178**:1, 1938.

121. Zündel, W., and Jentsch, M.: Die allergischen Vorgänge beim Bäckerekzem und ihre Deutung, Arch. f. Dermat. u. Syph. **178**:469, 1939.

122. Tedder, J. W.: Toxic Manifestations in the Skin Following Sulfanilamide Therapy, Arch. Dermat. & Syph. **39**:217 (Feb.) 1939.

123. Hallam, R.: Severe Skin and General Reaction Following the Administration of M & B 693 and Exposure to Ultra-Violet Light, Brit. M. J. **1**:559, 1939.

124. Gallagher, J. R.: Sulfanilamide Drug Fever: A Second Attack of Sudden Onset, New England J. Med. **221**:132, 1939.

125. Rogers, E. B.: Sensitization Reaction to Sulfanilamide, J. A. M. A. **111**:2290 (Dec. 17) 1938.

126. Bowen, R.: Karaya Gum as a Cause of Urticaria, Arch. Dermat. & Syph. **39**:506 (March) 1939.

Insulin sensitiveness is of some practical importance because the cases are not rare. Kern and Langner [127] have studied the mechanism by which the condition develops, pointing out that it occurs more often in nondiabetic than in diabetic persons, for, as is usual in cases of drug allergy, the classic method of producing sensitiveness is to provide for two courses of treatment with an interval between. The treatment of insulin hypersensitiveness does not appear to be difficult. In Corcoran's [128] patient urticaria developed, but with a series of doses given a few minutes apart, at first intracutaneously, than subcutaneously and finally intravenously, desensitization was accomplished in about fifteen hours. Ulrich, Hooker and Smith [129] had a similar experience, for repeated desensitization with doses given at intervals of thirty to sixty minutes changed the reaction so that, whereas the first dose of 0.1 cc. caused a large wheal 23 by 33 mm. in diameter at 10:30 a. m., the thirteenth dose, consisting of twice the quantity, produced no reaction at all at midnight. As a matter of fact, one would suppose that the routine method by which insulin is given in one or two doses each day would be the ideal treatment for any sensitiveness to it.

OTHER ALLERGIC DISEASES OF THE SKIN

Sensitivity to poison ivy has been studied. As Simon and Lotspeich [130] point out, sensitiveness does not occur in all persons exposed, and so must depend on a predisposing factor. Specific treatment is sometimes helpful from the clinical point of view, but the fact is that cutaneous tests made by a careful technic with serial dilutions of ivy extract showed that the treatment had produced little difference in the strength of the reaction afterward. Zisserman and Birch [131] observed 304 boys at a scout camp who were treated with an ether extract of poison ivy suspended in olive oil. In spite of treatment, 51.6 per cent of the boys had dermatitis. A control group of 241 boys were found from their histories to be susceptible to poison ivy, but were nevertheless left untreated. Of this group dermatitis occurred in 60.6 per cent. The differences between the groups were small.

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127. Kern, R. A., and Langner, P. H.: Protamine and Allergy: I. Nature of the Local Reactions After Injections of Protamine Zinc Insulin; II. Induction of Sensitivity to Insulin by Injections of Protamine Zinc Insulin, J. A. M. A. **113**:198 (July 15) 1939.

128. Corcoran, A. C.: Note on the Rapid Desensitization in a Case of Hypersensitiveness to Insulin, Am. J. M. Sc. **196**:359, 1938.

129. Ulrich, H.; Hooker, S. B., and Smith, H. H.: Allergic Reaction to Insulin: Report of a Case, New England J. Med. **221**:522, 1939.

130. Simon, F. A., and Lotspeich, E.: Observations on Sensitivity to Poison Ivy, J. Invest. Dermat. **2**:143, 1939.

131. Zisserman, L., and Birch, L.: The Prophylaxis and Treatment of Poison Ivy Dermatitis with an Extract of Rhus Toxicodendron, J. Allergy **10**:596, 1939.

Meantime, Landsteiner and Chase [132] have studied the question of how the whole skin becomes sensitive. They repeated Strauss's original experiment, except that this time the isolated islands of skin to be tested were separated by a deep incision involving the muscular layer, and therefore cutting the lymphatics which lie between this muscle and the skin itself. When this was done, the sensitiveness produced on the treated island did not spread beyond it. This and other experiments show that sensitiveness to poison ivy spreads through the lymphatics and not by direct contact between one skin cell and the next.

Atopic dermatitis is that form of so-called eczema which has a typical distribution to the face, neck and cubital and popliteal spaces and which is associated with positive cutaneous reactions and the presence of passive transfer bodies in the blood. Its mechanism appears to be comparable with that of hay fever and asthma, and the condition can be conceived of as "asthma of the skin." The cause of trouble comes not by direct contact but through the blood vessels underneath the skin. In children at least, foods often appear to be the offending substances, and the elimination of eggs, or perhaps milk, has given relief in a number of cases. In view of its blood-borne cause of the condition, it is not surprising that Feinberg,[133] as well as Osborne and Walker,[134] states that dusts can cause atopic dermatitis. Feinberg has studied 14 patients who gave a definite seasonal history of dermatitis and in whom cutaneous tests showed positive reactions to pollens and to fungi. They were benefited greatly by treatment. I, too, have seen such patients and have found that, in addition to pollen, the other dust substances of domestic origin—kapok and cottonseed, as well as the animal danders—are occasional causes of atopic dermatitis.

Fungous dermatitis can give a clinical picture which is almost indistinguishable from that of contact dermatitis and of atopic dermatitis. Moreover, any two, or even all three, of these conditions can coexist in the same patient. The literature on this problem is large, too large to review here, particularly as an excellent analysis has recently been presented by Goodman and Sulzberger.[135] Two papers seem to be of practical value. Berberian [136] found that if socks made of silk, wool or

132. Landsteiner, K., and Chase, M. W.: Studies on the Sensitization of Animals with Simple Chemical Compounds: VI. Experiments on the Sensitization of Guinea Pigs to Poison Ivy, J. Exper. Med. **69**:767, 1939.

133. Feinberg, S. M.: Seasonal Atopic Dermatitis: The Role of Inhalant Atopens, Arch. Dermat. & Syph. **40**:200 (Aug.) 1939.

134. Osborne, E. D., and Walker, H. L.: Contact and Environmental Allergens as a Cause of Eczema in Infants and in Children, Arch. Dermat. & Syph. **38**:511 (Oct.) 1938.

135. Goodman, J., and Sulzberger, M. B.: Allergy in Dermatology, J. Allergy **10**:481, 1939.

136. Berberian, D. A.: Dermatophytosis of Feet: Sources and Methods of Prevention of Reinfection, Arch. Dermat. & Syph. **38**:367 (Sept.) 1938.

cotton are placed in a flask of water and are incubated, the fungus can be cultivated easily. Inner soles and even leather itself make a good substrate for the growth of the fungus. Ordinary laundering has no effect on it, but exposure to formaldehyde vapor for as short a time as twelve hours is sufficient to kill the organisms in shoes and socks. Cutaneous tests with fungus extracts produce allergic reactions of the delayed inflammatory tuberculin type. Lewis, MacKee and Hopper [137] declare that positive reactions can always be obtained in the presence of a dermophytid or of an acute inflammatory lesion of fungous origin. More important, however, is the second statement that a negative reaction rules out a mycotic cause. The difficulty, however, is that the test is specific, and so its result must depend on the genus of the causative organism and, consequently, on the nature of the test material.

At the end of this rapid and sketchy review, in which it is quite impossible to touch any but the "high spots," it is most appropriate to quote a sentence from that remarkable autocrat Dr. Oliver Wendell Holmes, who declared: "Knowledge and timber shouldn't be used till they are seasoned."

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137. Lewis, G. M.; MacKee, G. M., and Hopper, M. E.: The Trichophytin Test: Its Value as a Diagnostic Aid, Arch. Dermat. & Syph. **38**:713 (Nov.) 1938.

Obituaries

HARVEY CUSHING, M.D.

1869-1939

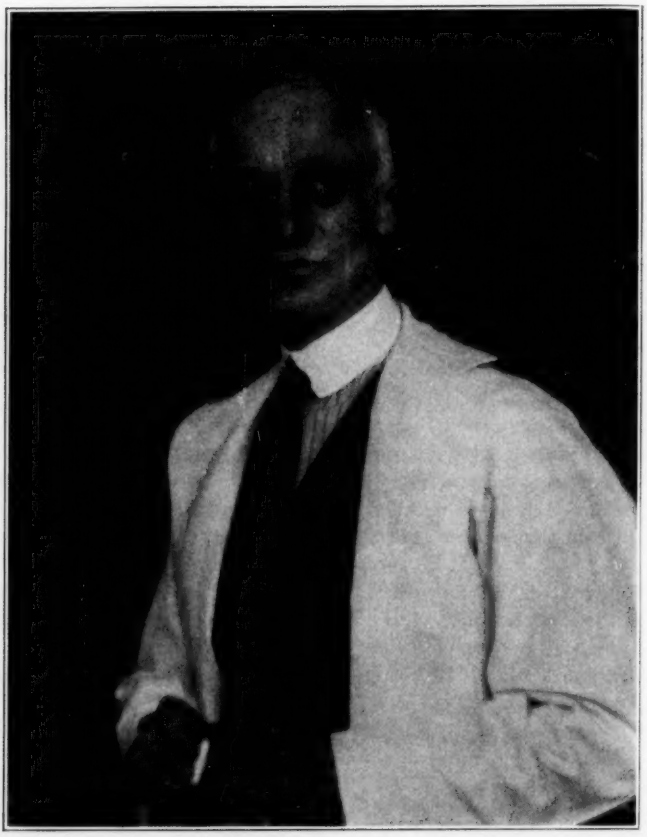
The editorial board of the Archives feels a distinct sense of personal loss in the death of Dr. Harvey Cushing. He was a contributor to our journal from time to time,[1] in 1927 with L. M. Davidoff, in 1932 with M. N. Fulton, and in 1933 when he submitted for publication " 'Dyspituitarism': Twenty Years Later," a Harvey Society lecture in which he described his own conception of the clinical aspects of pituitary basophilism. He was one of our meticulous critics, making no bones about his dislike for certain of our peculiarities of spelling, punctuation or syntax. But at the same time he was a staunch friend: the first to congratulate us on work well done, the last to criticize our failings behind our back, and always one of our sincerely interested, inquisitive readers.

Dr. Cushing, as every one knows, was a doctor of unusual versatility. He was a distinguished brain surgeon, the most distinguished in the world of his time, founder of a whole school of neurosurgeons whose accomplishments now encircle the globe. He was an imaginative clinical investigator. He was an expert medical bibliophile and historian. He was an eminent teacher. He was a fine writer, and hence was adroit with both the scalpel and the pen, as President Lowell aptly said in awarding him an honorary degree at Harvard. This was no perfunctory compliment suitable to the occasion and meaning little else, for Dr. Cushing's nonmedical writings—the "Life of Sir William Osler" (1925), "Consecratio Medici and Other Papers" (1928), and "From a Surgeon's Journal 1915-1918" (1936)—have interested a wide range of readers, have inspired medical students almost as much as did Cushing's skill in the operating room and have stimulated many a doctor to better literary efforts.

Dr. Cushing was never conceited or boastful of his reputation as an author. Two years ago he answered a friend, in reply to a request for a copy of his complete bibliography: "You will remember how horrified

1. Cushing, H., and Davidoff, L. M.: Studies in Acromegaly: IV. The Basal Metabolism, Arch. Int. Med. **39**:673-697 (May) 1927. Davidoff, L. M., and Cushing, H.: Studies in Acromegaly: VI. The Disturbances of Carbohydrate Metabolism, ibid. **39**:751-779 (June) 1927. Fulton, M. N., and Cushing, H.: The Specific Dynamic Action of Protein in Patients with Pituitary Disease, ibid. **50**: 649-667 (Nov.) 1932. Cushing, H.: "Dyspituitarism": Twenty Years Later, with Special Consideration of the Pituitary Adenomas, ibid. **51**:487-557 (April) 1933.

Osler was, shortly before his end, to receive Miss Minnie Blogg's published list of his bibliography. I have much the same feeling about my own past papers, many of which were ephemeral and written only because I got pushed into contributing something for a medical meeting



HARVEY CUSHING, M.D.
1869-1939

here and there. As a matter of fact, I think you have all the original papers bound from 1920 to 1933; and of those written before and since that time, the less said the better."

Dr. Cushing took chief pride in being a clinician. He once said with deep feeling, when he suspected that the laboratory side of medicine

was becoming overemphasized, "We have instruments of precision in increasing numbers with which we and our hospital assistants at untold expense make tests and take observations, the vast majority of which are but supplementary to, and as *nothing* compared with, the careful study of the patient by a keen observer using his eyes and ears and fingers and a few simple aids. The practice of medicine is an art and can never approach being a science even though it may adopt and use for its purposes certain instruments originally designed in the process of scientific research."[2] These words summarized his own philosophy as to how the advancement of medical knowledge could best be obtained; in his own clinical work he steadily maintained this viewpoint and taught it to his assistants.

The copy of Morgan's "Discourse upon the Institution of Medical Schools in America" in his library had come to him directly from his great-grandfather, Dr. David Cushing, through the hands of his grandfather, Dr. Erastus Cushing, his father, Dr. Henry Cushing, and his brother, Dr. Edward Cushing. Dr. Harvey Cushing would ask no higher compliment than to be thought of as one of the medical profession who did his job as best he could, at last achieving an honorable place beside the other medical members of his family in that select company of practitioners whose work makes them forever to be respected.

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2. Cushing, H.: Medicine at the Crossroads, J. A. M. A. **100**:1567-1575 (May 20) 1933.

Book Reviews

Der Magenkrebs. By Georg Ernst Konjetzny, M.D., Professor of Surgery of Hansische University, Hamburg, Germany. Cloth. Price, 26.80 marks. Pp. 289, with 155 illustrations. Stuttgart: Ferdinand Enke, 1938.

This book will be welcomed by every one interested in the subject of gastric cancer, for it contains the results of Konjetzny's life work. The author is a recognized authority, and in this volume he presents new material and fits it together with older observations to present a complete picture, not only of the development of gastric carcinoma but of present day therapeusis of the most common visceral malignant change. In view of the impossibility of preventing cancer, early diagnosis and radical surgical measures are needed.

There is a certain inherited tendency or organic disposition to carcinoma, but cancer as such is not inherited. Cancer is apparently neither contagious nor infectious. The Cohnheim theory of development from immature embryonal cells has been discarded. Trauma is not significant except as it relates to the results of destruction of the mucosa, as in acid or alkali poisoning, with subsequent regeneration and heteroplasia. Konjetzny accepts the Virchow theory of the role of local disease processes in the development of tumors and devotes a considerable portion of the monograph to the thesis that the chronic inflammatory conditions of great significance as a basis for carcinoma are chronic gastritis with its sequelae and gastric ulcer. Konjetzny has spent thirty years working on the relation between chronic gastritis, benign ulcer and carcinoma. Gastritis is thought by him to be the basis for both ulcer and carcinoma. Gastric carcinoma is always associated with definite chronic atrophic or atrophic-hyperplastic gastritis and never appears in a perfectly normal mucosa. The important process is the regeneration in the mucosa resulting from the chronic inflammation. The transition from gastritis to polyp formation and carcinoma is illustrated in detail. The carcinomatous change is thought to be multicentric, taking place in the cells of a broad area of the mucosa.

It is not possible by clinical methods alone to demonstrate the carcinomatous transformation of a benign ulcer. The histologic evidence is more definite, although difficulties exist there also. The diagnosis must be deduced from a careful analysis of all the evidence, for no single finding is pathognomonic. Carcinoma may arise in the edge of an ulcer or in the neighboring mucosa independent of the ulcer and because of the gastritis. The gastritis associated with ulcer is perhaps somewhat more acute than that associated with carcinoma, but on the whole there is little, if any, difference between the two types.

The histologic types of carcinoma are variable, are not to be correlated with the gross appearances and from a clinical standpoint are not significant. The gross forms are of prognostic importance. The polypoid intraluminal tumors and the ulcerated dishlike well walled-off growths do not usually metastasize as early as those in which the infiltration extends indefinitely out beyond an area of ulceration or those in which there is no ulceration but mere diffuse infiltration.

Treatment should be directed toward early and radical resection in all cases of carcinoma and of such precarcinomatous states as polypoid gastritis. Konjetzny urges a thorough investigation, including fecal and gastric analysis and roentgen and gasroscopic examination, of all patients with digestive symptoms. Exploratory laparotomy as a diagnostic procedure is not justifiable because of the high degree of reliability of the other clinical methods. Small carcinomas often cannot be palpated. Hence, all areas clinically suspicious should be resected. The only contraindication to resection of gastric carcinoma is the presence of proved distant metastases or extensive carcinomatous peritonitis. Undue pessimism is not justi-

fiable even in regard to the younger patients. In the Breslau (Germany) Clinic the longest cure (twenty-one years) occurred in a man operated on at the age of 31. Significant palliative effects may be obtained even when Krukenberg tumors are present.

The Principles and Practice of Medicine, Designed for the Use of Practitioners and Students of Medicine. Originally written by the late Sir William Osler, Bart., M.D., F.R.T.P., F.R.S., formerly Regius Professor of Medicine, Oxford University; Professor of Medicine, Johns Hopkins University; Professor of the Institute of Medicine, MacGill University; Professor of Clinical Medicine in the University of Pennsylvania. Revised by Henry A. Christian, M.D., LL.D., S.D., F.R.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard University; Physician in Chief, Peter Bent Brigham Hospital. (The ninth, tenth, eleventh and twelfth editions of this book were revised by Thomas McCrae, M.D., F.R.C.P., formerly Professor of Medicine of Jefferson Medical College, Philadelphia). Thirteenth edition. Price, $9. Pp. 1,450, illustrated. New York: D. Appleton-Century Company, Inc., 1938.

From the time of its first appearance in 1892, Osler's "Principles and Practice of Medicine" has been the most valued guide to the practice of medicine in the English language. Its use as a reference has been worldwide. This prestige has been maintained through subsequent editions prepared under Dr. Osler's hand and later under the hand of his student and friend Dr. McCrae. The new thirteenth edition is prepared by another former pupil and friend, Dr. Henry A. Christian, and fully maintains the standard set by the former editions. It is inevitable that extensive changes should be made. The text has been rewritten in part, to include the most recent advances in medical knowledge and practice. Some portions have been deleted, and extensive changes made which Dr. Osler would have been the first to make had he been preparing the edition. A student of the earlier text may feel a little strange to open at pneumonia instead of typhoid and not to find other subjects in their accustomed places. But the book has been rearranged and rewritten with a sympathetic understanding of the broad aims of Dr. Osler's first text and, in spite of changes, adheres to the Osler tradition. The volume offers the advantage of a uniformity of point of view and teaching which only a text written by one man can offer, and its value is further enhanced by the clinical experiences and broad scholarship of Dr. Christian.

A Guide to Human Parasitology for Medical Practitioners. By D. B. Blacklock, M.D. (Edinburgh); D.P.H. (London); D.T.M. (Liverpool), Professor of Tropical Hygiene, Liverpool School of Tropical Medicine, University of Liverpool, formerly Professor of Parasitology, and Director of the Sir Alfred Lewis Jones Laboratory, Freetown, Sierra Leone, West Africa; and T. Southwell, D.Sc., Ph.D., A.R.C.Sc., F.Z.S., F.R.S.E., Walter Myers Lecturer in Parasitology, School of Tropical Medicine, University of Liverpool; formerly Director of Fisheries to the Governments of Bengal and Bihar and Orissa; Scientific Advisor and Inspector of Pearl Banks to the Ceylon Company of Pearl Fishers, and Honorary Assistant, Zoological Survey of India. Third edition. Price, $4. Two colored plates and 122 illustrations. Baltimore: William Wood & Company, 1938.

This volume has been prepared for ready reference on the subject of human parasitology by the practicing physician. This purpose it fulfils admirably. As is inevitable when so broad a subject is to be presented in one small volume, a rather limited consideration must be given to each subject. A few minor omissions might have been made to allow more space for the subject in hand.

It would seem hardly necessary in a book prepared for physicians to waste space on a chapter devoted to the care and use of the microscope or to include even an abbreviated consideration of blood examination. Also the group of spiro-

chaetacia should have been left to the bacteriologist. This space could have been used advantageously in expanding a valuable text on the subject of animal parasites.

A bibliography which would include not only the larger texts but detailed references to the special subject for students would be an advantage. The book as it is is clear and comprehensive and is of value to the practitioner for whom it is designed.

Fundamentals of Experimental Pharmacology. By Torald Sollmann and Paul J. Hanzlik. Second edition. Price, $4.25. Pp. 307, with illustrations. San Francisco: J. W. Stacey, Inc., 1939.

The second edition of this well known manual does not differ in form or general arrangement from the first. Structural formulas for certain of the alkaloids have been changed to agree with present day views. Experiments with recently introduced drugs—evipal, pentobarbital, avertin with amylene hydrate and sulfanilamide—have been added. One of the most valuable features of both the first edition and the older manual of the senior author which preceded it is the table of doses suitable for laboratory animals. The new edition extends the list considerably and contains a tremendous amount of material that is elsewhere scattered through an extensive literature. Many of the doses have been confirmed in the laboratories of the authors. Few errors have been noted by this reviewer, the most serious one being the statement that digitalis is said to be assayed against ouabain in the eleventh revision of the United States Pharmacopeia. Ouabain has been retained as a standard for strophanthin but not for digitalis. Probably no active laboratories of pharmacology in this country have been without the predecessor of this manual, and it is likely that the present edition will maintain the status of the first.

Affections non ulcéreuses du duodenum. By I. Pavel and A. Paunesco-Podeano. Paper. Price, 50 francs. Pp. 204, with 57 illustrations. Paris: Masson & Cie, 1938.

This publication of Pavel and Paunesco-Podeano on nonulcerative diseases of the duodenum is unique. The authors include discussions of normal and abnormal physiology of the duodenum along with fairly complete descriptions of nonulcerative duodenal clinical syndromes and their treatment. Among the conditions presented are pseudoulcerative duodenitis, hemorrhagic duodenitis, chronic duodenitis with icterus, phlegmonous duodenitis, diverticulation of the duodenum, duodenal stasis (mechanical and functional) and tumors and congenital malformations of the duodenum. Each condition is presented in routine textbook fashion, with a tendency to emphasis on the clinical aspects. Each chapter is concluded with an extensive and predominantly European bibliography on its subject.

The monograph deserves a high place among those on various phases of gastroenterology. It is a good collection of practical data on nonulcerative duodenal disease. Every one interested in internal medicine, and especially in gastroenterology, will find many helpful clinical ideas.

Marihuana, America's New Drug Problem: A Sociologic Question with Its Basic Explanation Dependent on Biologic and Medical Principles. By Robert P. Walton, Professor of Pharmacology, School of Medicine, University of Mississippi, with a foreword by E. M. K. Geiling, Professor of Pharmacology, University of Chicago, and a chapter by Frank R. Gomila, Commissioner of Public Safety, New Orleans, and M. C. Gomila Lambou, Assistant City Chemist. Cloth. Price $3. Pp. 223, with 17 figures and illustrations. Philadelphia: J. B. Lippincott Company, 1938.

Knowledge concerning the drug problem presented by marihuana has come to most physicians through the somewhat sensational news stories in the supplements

of the Sunday newspapers. Dr. Walton's exhaustive monograph concerning the narcotic principles of the drug is extremely timely. The book is factual but interestingly written. It covers the historical, botanic, pharmacologic, sociologic, legal and public health aspects of the use, or more specifically the misuse, of marihuana. There is a valuable chapter on nomenclature, which gives a complete glossary. The bibliography contains 419 references. The book should prove an invaluable reference for sociologists, public health officers and physicians.

The Genuine Works of Hippocrates. Translated from the Greek by Francis Adams. Price, $3.00. Pp. 384, with 8 plates. Baltimore: The Williams & Wilkins Co., 1939.

The reviewer is unable to discuss critically the merit of various Hippocratic texts and translations, but from the standpoint of the bibliophile one can only be pleased with this handsome edition of the Adams version. The book is well printed on fine paper and in general is obviously a superior piece of book making. The publishers are to be congratulated.

Notices

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Requests have been received for a twenty year index of the ARCHIVES OF INTERNAL MEDICINE. Before serious consideration is given to the production of a cumulated index, it is desirable to know whether the demand for it would be sufficient to warrant its sale at not to exceed $5 a copy. It will be appreciated if those who are interested in such an index will fill out and send the form which appears below to the Managing Editor at the publication office, 535 North Dearborn Street, Chicago.

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